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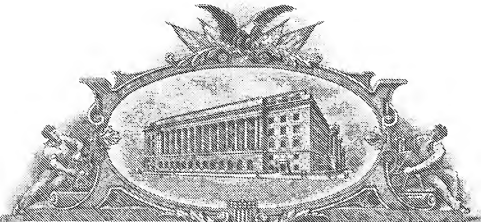

1321542

THE UNITED STATES OF AMERICA

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UNITED STATES DEPARTMENT OF COMMERCE

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May 17, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/543,176***
FILING DATE: ***February 10, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/04872***

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Express Mail Label No.: EI 992 784 045 US

PATENT

Attorney Docket No.: **PRF-08760**

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. 1.53(b)(2).

Docket Number	PRF-08760	Type a plus sign (+) inside this box →	+

INVENTOR(s) / APPLICANT(s)

Last Name	First Name	Middle Initial	Residence (City and Either State or Foreign Country)
Liu	**Shuang**		**West Lafayette, IN 47906**
He	**Zhengjie**		**West Lafayette, IN 47906**

TITLE OF THE INVENTION (280 Characters Max.)

Crowned Dithiocarbamate Metal Complex Pharmaceuticals

CORRESPONDENCE ADDRESS

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
United States of America

22581 US.PTO 60/543176 021004

ENCLOSED APPLICATION PARTS *(Check All That Apply)*

X	Specification	Number of Pages	**74**	__	Small Entity Statement
X	Drawing(s)	*Number of Sheets*	**0**	__	Other (Specify): Power of Attorney
				__	Other (Specify): Assignment

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

__	Charge Account No. **08-1290** in the amount of **$80.00. An originally executed duplicate of this transmittal is enclosed for this purpose.**	FILING FEE AMOUNT ($)	**$80.00**
X	The Commissioner is hereby authorized to charge any deficiency in the payment of the required fee(s) and/or credit any overpayment to Deposit Account No.: **08-1290. An originally executed duplicate of this transmittal is enclosed for this purpose.**		

This invention was made by an agency of the United States Government under a contract with an agency of the United States Government.

X No.
__ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

Date: February 10, 2004

Jason R. Bond
Reg. No.: 45,439
MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
(608) 218-6900

__ Additional inventors are being named on separately numbered sheets attached hereto.

Express Mail Label No.: **EL 992 784 045 US**

PATENT
Attorney Docket No.: **PRF-08760**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Shuang Liu.

For: **Crowned Dithiocarbamate Metal Complex Pharmaceuticals**

Mail Stop Provisional Patent Application
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION UNDER 37 C.F.R. § 1.10

I hereby certify that this correspondence and the documents referred to as attached therein are being deposited with the United States Postal Service on **February 10, 2004**, in an envelope as "EXPRESS MAIL POST OFFICE TO ADDRESSEE" service under 37 C.F.R. § 1.10, Mailing Label Number **EL 992 784 045 US** addressed to: **Mail Stop Provisional Patent Application**, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-01450

Jennifer B. Xistris

TRANSMITTAL COVER SHEET FOR FILING PROVISIONAL APPLICATION (37 C.F.R. § 1.51(2)(i))

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 C.F.R. 1.53(b)(2).

1. The following comprises the information required by 37 C.F.R. § 1.51(a)(2)(i)(A):

2. The name(s) of the inventor(s) is/are (37 C.F.R. § 1.51(a)(2)(i)(B)):

   Shuang Liu
   Zhengjie He

3. Address(es) of the inventor(s), as numbered above (37 C.F.R. § 1.51(a)(2)(i)(C)):

   3304 Jasper St., West Lafayette, Indiana 47906
   170 Burke Court, Apt. 312, West Lafayette, Indiana 47906

4. The title of the invention is (37 C.F.R. § 1.51(a)(2)(i)(D)):

   Crowned Dithiocarbamate Metal Complex Pharmaceuticals

5. The name, registration, and telephone number of the attorney (*if applicable*) is (37 C.F.R. § 1.51(a)(2)(i)(E)):

Jason R. Bond
Reg. No.: 45,439
Tel.: (608) 218-6900

(complete the following, if applicable)

__ A Power of Attorney accompanies this cover sheet.

6. The docket number used to identify this application is (37 C.F.R. § 1.51(a)(2)(i)(F)):

Docket No.: **PRF-08760**

7. The correspondence address for this application is (37 C.F.R. § 1.51(a)(2)(i)(G)):

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105

8. Statement as to whether invention was made by an agency of the U.S. Government or under contract with an agency of the U.S. Government. (37 C.F.R. § 1.51(a)(2)(i)(H)):

This invention was made by an agency of the United States Government, or under contract with an agency of the United States Government.

X No.

__ Yes.

The name of the U.S. Government agency and the Government contract number are: _____.

9. Identification of documents accompanying this cover sheet:

A. Documents required by 37 C.F.R. § 1.51(a)(2)(ii)-(iii):

Specification: No. of pages **74**

Drawings: No. of sheets **0**

B. Additional documents:

X Claims: No. of claims **49**

__ Power of Attorney

__ Small Entity Statement

__ Assignment

__ Other

10. Fee

The filing fee for this provisional application, as set in 37 C.F.R. § 1.16(k), is $160.00, for other than a small entity, and $80.00, for a small entity.

X Applicant is a small entity.

11. Small Entity Statement

__ The verified statement(s) that this is a filing by a small entity under 37 C.F.R. §§ 1.9 and 1.27 is(are) attached.

12. Fee payment being made at this time

__ Charge Account No. **08-1290** in the amount of **$80.00. An originally executed duplicate of this transmittal is enclosed for this purpose.**

13. Method of Fee Payment:

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__ Charge Account No. **08-1290**, in the amount of **$80.00. A duplicate of this Cover Sheet is attached.**

X Please charge Account No. **08-1290** for any fee deficiency. **A duplicate of this Cover Sheet is attached.**

Date: February 10, 2004

Jason R. Bond
Reg. No.: 45,439

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101 Howard Street, Suite 350
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(608) 218-6900

Crowned Dithiocarbamate Metal Complex Pharmaceuticals

FIELD OF THE INVENTION

The present invention relates to compositions comprising crowned dithiocarbamate metal complexes and methods of using these compositions. In particular, the present invention relates to neutral and cationic radioactive metal-nitrido complexes of crowned dithiocarbamates (DTCs), and methods of using these complexes as radiopharmaceuticals for diagnosis and treatment of cardiovascular disorders, infectious disease, and cancer. The present invention also relates to tripodal chelator-metal complexes of crowned DTCs and methods of using these complexes for treating diseases such as those characterized by nitric oxide overproduction. The present invention further relates to the use of crowned DTCs for heavy metal detoxification.

BACKGROUND OF THE INVENTION

Since early 1980s, extensive research efforts have been directed towards the development of lipophilic ^{99m}Tc complex cations as heart imaging agent (Nun, A. D. *Semin. Nucl. Med.* 1990, 20, 111). As a result of these efforts, two cationic ^{99m}Tc complexes (^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin) have been approved as commercial radiopharmaceuticals for myocardial perfusion imaging. Q3 and Q12 are cationic ^{99m}Tc complexes containing two monodentate phosphine ligands and a tetradentate Schiff-base chelator. Lipophilic ^{99m}Tc complexes, such as ^{99m}Tc-N-Noet, with neutral charge have also been studied for myocardial perfusion imaging. ^{99m}Tc-N-Noet is still under clinical investigation in Europe. Perfusion is defined as blood flow at the cellular level - the delivery of nutrients and removal of waste products to maintain cellular function (Dilsizian, V. *J. Nucl. Cardiol.* 2000, 7, 180; Marmion M. and Deutsch, E. *Quart. J. Nucl. Med.* 2000, 7, 701). An ideal myocardial perfusion agent should have a high first-pass extraction with stable myocardial retention, which linearly tracks myocardial blood flow over a wide range. Hepatic and gastrointestinal uptake should be minimal with exercise as well as with pharmacological stress and rest studies. The agent may redistribute; but should be in a predictable and reliable manner (Saha, G. B. et al *Nucl. Med. Biol.* 1992, 19, 1; Jain, D. *Semin. Nucl. Med.* 1999, 29, 221; Banerjee, S. et al *Semin. Nucl. Med.* 2001, 31: 260). Despite the widespread use of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin in myocardial perfusion imaging studies, they do not meet the requirements of an ideal perfusion imaging agent mainly due to the low first-pass

extraction, flow-dependence and high uptake in liver and lungs. Therefore, there is still a continuing need for the development of better radiotracers for myocardial perfusion imaging.

SUMMARY OF THE INVENTION

The present invention provides compositions comprising crowned dithiocarbamate metal complexes and methods of using these compositions. In particular, the present invention provides neutral and cationic radioactive metal-nitrido complexes of crowned dithiocarbamates (DTCs), and methods of using these complexes as radiopharmaceuticals for diagnosis and treatment of cardiovascular disorders, infectious disease, and cancer. The present invention also provides tripodal chelator-metal complexes of crowned DTCs and methods of using these complexes for treating diseases such as those characterized by nitric oxide overproduction. The present invention further provides methods of using crowned DTCs for heavy metal detoxification.

In some embodiments, the present invention provides compositions comprising a compound comprising the following formula: $(M{\equiv}N)L^1$ and pharmaceutically acceptable salts thereof; wherein N is Nitrogen; wherein M is a transition metal; and wherein L^1 is a first crowned dithiocarbamate, wherein the first crowned dithiocarbamate comprises a first crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2. In preferred embodiments, the transition metal is covalently bound to the first crowned dithiocarbamate.

In some embodiments, the present invention provides methods for radioimaging a subject (e.g. human) comprising; a) providing; i) a subject, and ii) a composition comprising a compound comprising the following formula: $(M{\equiv}N)L^1$ and pharmaceutically acceptable salts thereof; wherein N is Nitrogen; wherein M is a radioactive transition metal; and wherein L^1 is a first crowned dithiocarbamate, wherein the first crowned dithiocarbamate comprises a first crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2; b) administering the composition to the subject, and c) scanning at least a portion of the subject using a radioimaging device. In certain embodiments, at least a portion of the subject is tissue suspected of being diseased. In other embodiments, the at least a portion of the subject is myocardial tissue. In particular embodiments, the subject is a mammal (e.g. cat, dog, pig, horse, and preferably a human).

In certain embodiments, the first crowned dithiocarbamate comprises the following formula:

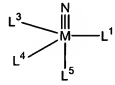
and pharmaceutically acceptable salt thereof, wherein R^1 or R^2 comprises the first crown ether-containing group, or R^1 and R^2 together comprise the first crown ether-containing group.

In other embodiments, the compound further comprises L^2 and comprises the following formula:$(M\equiv N)L^1L^2$ and pharmaceutically acceptable salts thereof; wherein L^2 is a second crowned dithiocarbamate, wherein the second crowned dithiocarbamate comprises a second crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2. In preferred embodiments, the transition metal is covalently bound to the first and second crowned dithiocarbamates.

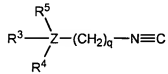
In additional embodiments, the second crowned dithiocarbamate comprises the following formula:

and pharmaceutically acceptable salt thereof, wherein R^1 or R^2 comprises the second crown ether-containing group, or R^1 and R^2 together comprise the second crown ether-containing group.

In some embodiments, the compound further comprises L^3, L^4, and L^5 and comprises the following formula:

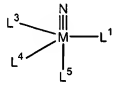


and pharmaceutically acceptable salts thereof; wherein L^3, L^4, and L^5 each comprise an isonitrile of the following formula:

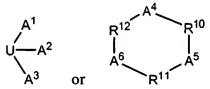


wherein q is 0 – 3; Z is carbon or silicon; R^3, R^4 and R^5 are the same or different, and are selected from: H, C_1-C_{10} alkyl substituted with 0 - 5 R^6, aryl substituted with 0-5 R^6, heteroaryl substituted with 0-5 R^6, and macrocyclic crown ether containing group 2 – 8 ether-oxygen atoms; wherein R^6 is selected from: H, OH, OR^7, $C(=O)OR^7$, $C(=O)NR^8R^9$, $PO(OR^8)_2$, $PO(NR^8R^9)_2$ and SO_2R^7; R^7, R^8 and R^9 are same or different, and are selected from: H, alkyl, aryl, and heteroaryl, or R^8 and R^9 together form a macrocyclic crown ether containing 2 – 8 ether-oxygen atoms.

In other embodiments, the compound further comprises L^3, L^4, and L^5 and comprises the following formula:



and pharmaceutically acceptable salts thereof; wherein L^3, L^4, and L^5 together form a tripodal chelator with the following formula:



wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles; A^4, A^5 and A^6 are selected from: NR^{14}, PR^{14}, S, and O; R^{10}, R^{11} and R^{12} are selected from a group of the formula:

$$-(CH_2)_g-,$$

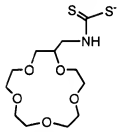
wherein g is 2 – 5; R^{13} is selected from: H, alkyl and aryl group; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl.

In certain embodiments, the transition metal is a radioactive metal. In particular embodiments, the transition metal is ^{99m}Tc or ^{94m}Tc. In other embodiments, the transition metal is ^{186}Re or ^{188}Re. In particular embodiments, subscript a in the formula of the first and/or second crown ether-containing group is 2, 3, 4, or 5. In other embodiments, subscript a in the formula of the first and/or second crown ether-containing group is 2 or 3. In certain embodiments, subscript a in the formula of the first and/or crown ether-containing group is 2. In other embodiments, subscript b in the formula of the first and/or second crown ether-containing group is 3, 4, 5, 6, 7, or 8. In additional embodiments, subscript b in the formula

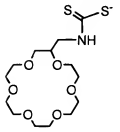
of the first and/or second crown ether-containing group is 3, 4, 5 or 6. In further embodiments, subscript c in the formula of the first and/or second crown ether-containing group is 2, 3, 4, or 5. In some embodiments, subscript c in the formula of the first and/or second crown ether-containing group is 2 or 3. In particular embodiments, subscript c in the formula of the first and/or second crown ether-containing group is 2.

In certain preferred embodiments of the compounds of the present invention M is ^{99m}Tc; a is 2 or 3; b is 3 – 6; c is 2 or 3; q is 1; Z is carbon; R^3, R^4 and R^5 can be the same or different, and are selected from: H, C_1-C_5 alkyl substituted with a R^6, aryl substituted with a R^6, heteroaryl substituted with a R^6, and macrocyclic crown ether containing 3 – 6 ether-oxygen atoms; R^6 is selected from: OR^8, $C(=O)OR^8$, $C(=O)NR^8R^9$, and $PO(NR^8R^9)_2$; R^7, R^8 and R^9 can be the same or different, and are selected from: H, alkyl, aryl, and heteroaryl, or R^8 and R^9 may be taken together to form a macrocyclic crown ether containing group 3 – 6 ether-oxygen atoms; A^1, A^2 and A^3 are selected from a group: imidazoly, pyrazoly, oxazolinyl, methimazolyl, and pyridyl; A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S; g is 2 or 3; R^{13} is selected from: H, methyl, and phenyl; and R^{14} is ethyloxyethyl, ethoxylpropyl, methyoxyethyl, and methoxypropyl.

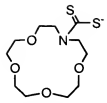
In some embodiments, the first and/or second crowned dithiocarbamate comprises



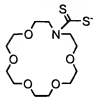
In other embodiments, the first and/or second crowned dithiocarbamate comprises



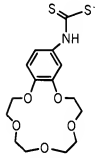
In certain embodiments, the first and/or second crowned dithiocarbamate comprises



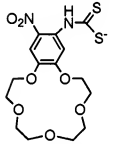
In additional embodiments, the first and/or second crowned dithiocarbamate comprises



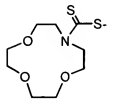
In other embodiments, the first and/or second crowned dithiocarbamate comprises



In some embodiments, the first and/or second crowned dithiocarbamate comprises



In particular embodiments, the first and/or second crowned dithiocarbamate is selected from



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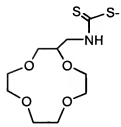
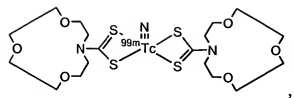


In some embodiments, the compound is selected from the group consisting of: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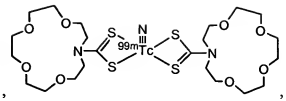
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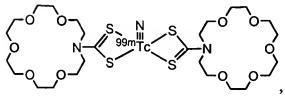
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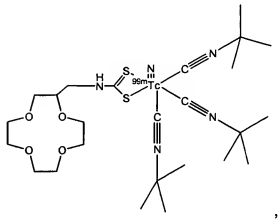
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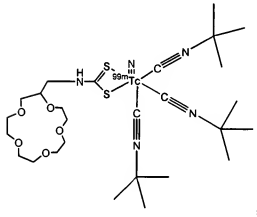
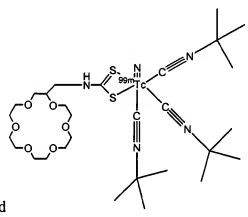
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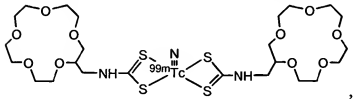
In other embodiments, the compound is selected from the group consisting of: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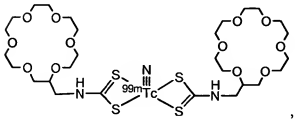
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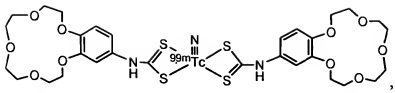
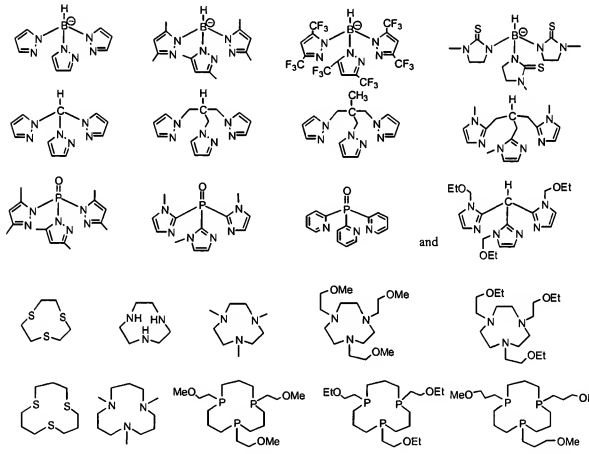
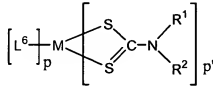


, and

In particular embodiments with a tripodal chelator, the tripodal chelator is selected from:

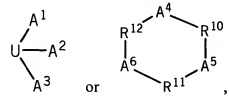


In some embodiments, the present invention provides compositions comprising the following formula:



, and pharmaceutically acceptable salt thereof,

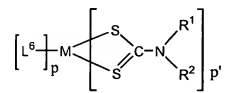
wherein M is a transition metal selected from: Fe(II), Fe(III), Mn(II), Mn(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ru(II), Ru(III), Pd(II), and Pt(II); p and p' are integers and are independently selected from 0 – 2; R^1 and R^2 comprises a crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2, or wherein R^1 and R^2 together comprise the crown ether-containing group; wherein L^6 is a tripodal chelator with a formula selected from:



, wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles; A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S; R^{10}, R^{11} and R^{12} are selected from a group of the formula: $-(CH_2)_g-$, wherein g is 2 – 5; R^{13} is selected from: H, alkyl and aryl group; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl.

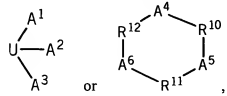
In other preferred embodiments, M is Ru(III); p is 1; p'is 2; R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is 2 or 3; b is 3 – 6; c is 2 or 3; A^1, A^2 and A^3 are selected from a group: imidazoly, pyrazoly, oxazolinyl, methimazolyl, and pyridyl; A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S; g is 2 or 3; R^{13} is selected from: H, methyl, and phenyl; and R^{14} is ethyloxyethyl, ethoxylpropyl, methyoxyethyl, and methoxypropyl; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl.

In some embodiments, the present invention provides methods of treating a disease resulting from overproduction of nitric oxide or reactive oxygen species, comprising; a) providing; i) a subject with a disease, and ii) a composition comprising a compound comprising the following formula:



, and pharmaceutically acceptable salt thereof, wherein M is a transition metal selected from: Fe(II), Fe(III), Mn(II), Mn(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ru(II), Ru(III), Pd(II), and Pt(II); p and p' are integers and are independently selected from 0 – 2; R^1 and R^2 comprises a crown ether-containing group of

the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2, or wherein R^1 and R^2 together comprise the crown ether-containing group; wherein L^6 is a tripodal chelator with a formula selected from:



, wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles; A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S; R^{10}, R^{11} and R^{12} are selected from a group of the formula: $-(CH_2)_g-$, wherein g is 2 – 5; R^{13} is selected from: H, alkyl and aryl group; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl; and b) administering the composition to the subject.

In some embodiments, the present invention provides methods of treating metal poisoning (metal detoxification), comprising; a) providing; i) a subject with metal poisoning, and ii) a composition comprising a crowned dithiocarbamate, wherein said crowned dithiocarbamate comprises a crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2, and administering said composition (or any other suitable composition described herein) to said subject.

In other embodiments, the present invention provides methods of making the compositions of the present invention comprising reacting pertechnetate with (1) a nitrido donor; (2) a reducing agent; (3) and a crowned DTC chelator. In a preferred embodiment, the nitrido donor is succinyl dihydride, and the reducing agent is stannous chloride. In some embodiments, the present invention provides kits for preparation of a radiopharmaceutical product of the present invention comprising: a) a first container (e.g. bottle) containing a nitrido donor, b) a second container (e.g. bottle) containing a stannous chloride and a chelating agent able to stabilize the tin cation, and c) a third container (e.g. bottle) containing a crowned DTC chelator as described herein. In certain embodiments, the present invention provides kits for preparation of a radiopharmaceutical product according to the present invention, comprising: a) a first container containing succinyl dihydride, and a stannous chloride and a chelating agent able to stabilize the tin cation, and b) a second container containing a crowned DTC chelator as described herein. In further embodiments, the kits comprise: a) a first container containing succinyl dihydride, stannous chloride and 1,2-

diaminopropane-N,N,N',N'-tetraacetic acid or a salt thereof, and b) a second container containing a crowned DTC chelator as described herein.

In further embodiments, the present invention provides kits comprising; a) one or more of the compositions of the present invention (e.g. as described above); and b) instructions for using the compound for a medical application (e.g. tissue imaging, treating a nitrous oxide related disease, or for metal detoxification). In certain embodiments, the compound is in a container (e.g. vial or bottle). In some embodiments, the instructions are written (e.g. on paper).

DEFINITIONS

To facilitate an understanding of the invention, a number of terms are defined below.

As used herein, the terms "subject" and "patient" refer to any animal, such as a mammal like a dog, cat, bird, livestock, and preferably a human.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring. The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14. When any variable (e.g., R^6) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are preferably stable compounds. When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the

rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example -CvFw where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom (preferably resulting in a stable structure). The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic

heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts

thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and

benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The coordination sphere of the radionuclide includes all the ligands or groups bound to the radionuclide. For a transition metal radionuclide to be stable it typically has a coordination number (number of donor atoms) comprised of an integer greater than or equal to 4 and less than or equal to 7; that is there are 4 to 7 atoms bound to the metal and it is said to have a complete coordination sphere. The requisite coordination number for a stable radionuclide complex is determined by the identity of the radionuclide, its oxidation state, and the type of donor atoms.

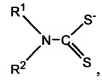
DESCRIPTION OF THE INVENTION

The present invention provides compositions comprising crowned dithiocarbamate metal complexes and methods of using these compositions. In particular, the present invention provides neutral and cationic radioactive metal-nitrido complexes of crowned dithiocarbamates (DTCs), and methods of using these complexes as radiopharmaceuticals for diagnosis and treatment of cardiovascular disorders, infectious disease, and cancer. The present invention also provides tripodal chelator-metal complexes of crowned DTCs and methods of using these complexes for treating diseases such as those characterized by nitric oxide overproduction. The present invention further provides methods of using crowned DTCs for heavy metal detoxification. The description of the invention provides further details on the compositions, kits and methods described above, and is provided below in the following sections: I) Exemplary Pharmaceutical Compositions; II) Therapeutic Uses; III) Methods of Making Crowned Dithiocarbamate Metal Complexes; and IV) Kits, Therapeutics Compositions and Routes of Administration.

I. Exemplary Pharmaceutical Compositions

Detailed below are certain exemplary pharmaceutical compositions of the present invention.

[1] In a first embodiment, the present invention provides a crowned DTC chelator of the formula:



and pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein

a is 2 – 5;

b is 3 – 8; and

c is 2 – 5.

[2] A preferred embodiment of the present invention is a crowned DTC chelator of embodiment [1], wherein:

a is 2 or 3;

b is 3 - 6; and

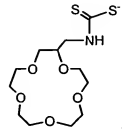
c is 2 or 3;

[3] A more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [2], wherein:

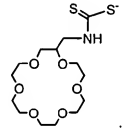
a is 2; and

c is 2;

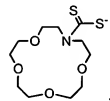
[4] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



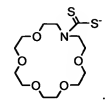
[5] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



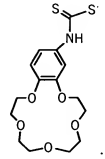
[6] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



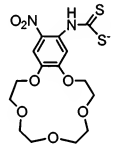
[7] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



[8] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



[9] Another more preferred embodiment of the present invention is a crowned DTC chelator of embodiment [3], that is:



[10] Another more preferred embodiment of the present invention is a method for preparation of a DTC chelator according to embodiments [1] – [9], comprising reacting amino crown ether with carbon disulfide in the presence of a base.

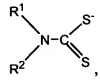
[11] In a second embodiment, the present invention provides a radiopharmaceutical of the formula:

$$(M{\equiv}N)L^1L^2,$$

and pharmaceutically acceptable salt thereof, wherein

M is a radionuclide selected from: ^{99m}Tc, ^{186}Re, and ^{188}Re;

L^1 and L^2 can be the same or different, comply with the formula:



R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein

a is 2 – 5;

b is 3 – 8; and

c is 2 – 5.

[12] A preferred embodiment of the present invention is a radiopharmaceutical of embodiment [11], wherein:

wherein M is ^{99m}Tc;

a is 2 or 3;

b is 3 - 6; and

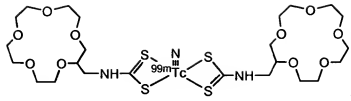
c is 2 or 3;

[13] A more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [12], wherein:

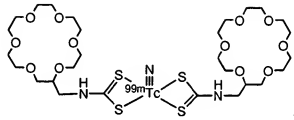
a is 2; and

c is 2;

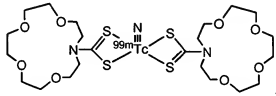
[14] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



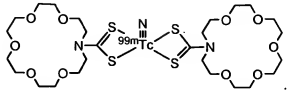
[15] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



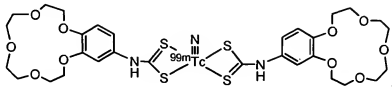
[16] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



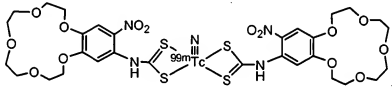
[17] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



[18] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



[19] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [13], that is:



[20] Another preferred embodiment of the present invention is a novel radiopharmaceutical composition containing a metal chelate according to embodiments [11] – [19].

[21] Another preferred embodiment of the present invention is a method for preparation of a radiopharmaceutical product according to embodiments [11] – [19], comprising reacting pertechnetate with (1) a nitrido donor; (2) a reducing agent; (3) and a crowned DTC chelator according to embodiments [1] – [19].

[22] Another preferred embodiment of the present invention is a method according to embodiment [27], wherein the nitrido donor is succinyl dihydride, and the reducing agent is stannous chloride.

[23] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiments [10] – [19], comprising:

a first bottle containing a nitrido donor,

a second bottle containing a stannous chloride and a chelating agent able to stabilize the tin cation, and

a third bottle containing a crowned DTC chelator according to embodiments [1] – [9].

[24] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiment [23], comprising:

a first bottle containing succinyl dihydride, a stannous chloride and a chelating agent able to stabilize the tin cation, and

a second bottle containing a crowned DTC chelator according to embodiments [1] – [9].

[25] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiment [24], comprising:

a first bottle containing succinyl dihydride, stannous chloride and 1,2-diaminopropane-N,N,N',N'-tetraacetic acid or a salt thereof, and

a second bottle containing a crowned DTC chelator according to embodiments [4] – [9].

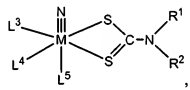
[26] Another preferred embodiment of the present invention is a novel radiopharmaceutical for radioimaging a mammal comprising (i) administering to said mammal an effective amount of a radiopharmaceutical of the formula according to embodiments [11] – [20], and (ii) scanning the mammal using a radioimaging device.

[27] In another preferred embodiment, the present invention provides a novel method for visualizing sites of myocardial disease in a mammal by radioimaging, comprising (i) administering to said mammal an effective amount of a radiopharmaceutical of

formula according to embodiments [11] – [20], and (ii) scanning the mammal using a radioimaging device.

[28] In another preferred embodiment, the present invention provides a novel method of diagnosing a myocardial disease in a mammal comprising administering to said mammal a radiopharmaceutical composition of formula according to embodiments [11] – [20], and imaging said mammal.

[29] In a third embodiment, the present invention provides a novel radiopharmaceutical of the formula:



,

and pharmaceutically acceptable salt thereof, wherein

M is a radionuclide selected from: ^{99m}Tc, ^{186}Re, and ^{188}Re;

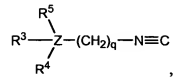
R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein

a is 2 – 5;

b is 3 – 8;

c is 2 – 5.

L^3, L^4 and L^5 can be the same or different, and are selected from an isonitrile of the formula:



,

wherein q is 0 – 3;

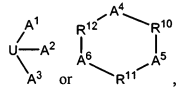
Z is carbon or silicon;

R^3, R^4 and R^5 can be the same or different, and are selected from: H, C_1-C_{10} alkyl substituted with 0 - 5 R^6, aryl substituted with 0-5 R^6, heteroaryl substituted with 0-5 R^6, and macrocyclic crown ether containing 2 – 8 ether-oxygen atoms;

R^6 is independently selected from: H, OH, OR^7, $C(=O)OR^7$, $C(=O)NR^8R^9$, $PO(OR^8)_2$, $PO(NR^8R^9)_2$ and SO_2R^7;

R^7, R^8 and R^9 can be the same or different, and are selected from: H, alkyl, aryl, and heteroaryl, or R^8 and R^9 may be taken together to form a macrocyclic crown ether containing 2 – 8 ether-oxygen atoms;

Alternatively L^3, L^4 and L^5 may be taken together to form a tripodal chelator of the formula:



,

wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O);

A^1, A^2 and A^3 can be the same or different, and are imine-N containing heterocycles;

A^4, A^5 and A^6 can be the same or different, and are selected from: NR^{14}, PR^{14}, S, and O;

R^{10}, R^{11} and R^{12} can be the same or different, and are selected from a group of the formula:

$$-(CH_2)_g-,$$

wherein g is 2 – 5;

R^{13} is selected from: H, alkyl and aryl group; and

R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl;

[30] A preferred embodiment of the present invention is a radiopharmaceutical of embodiment [29], wherein:

M is ^{99m}Tc;

a is 2 or 3;

b is 3 – 6;

c is 2 or 3;

q is 1;

Z is carbon;

R^3, R^4 and R^5 can be the same or different, and are selected from: H, C_1-C_5 alkyl substituted with a R^6, aryl substituted with a R^6, heteroaryl substituted with a R^6, and macrocyclic crown ether containing 3 – 6 ether-oxygen atoms;

R^6 is selected from: OR^8, $C(=O)OR^8$, $C(=O)NR^8R^9$, and $PO(NR^8R^9)_2$;

R^7, R^8 and R^9 can be the same or different, and are selected from: H, alkyl, aryl, and heteroaryl, or R^8 and R^9 may be taken together to form a macrocyclic crown ether containing 3 – 6 ether-oxygen atoms;

A^1, A^2 and A^3 are selected from a group: imidazoly, pyrazoly, oxazolinyl, methimazolyl, and pyridyl;

A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S;

g is 2 or 3;

R^{13} is selected from: H, methyl, and phenyl; and

R^{14} is ethyloxyethyl, ethoxylpropyl, methyoxyethyl, and methoxypropyl;

[31] A more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [30], wherein:

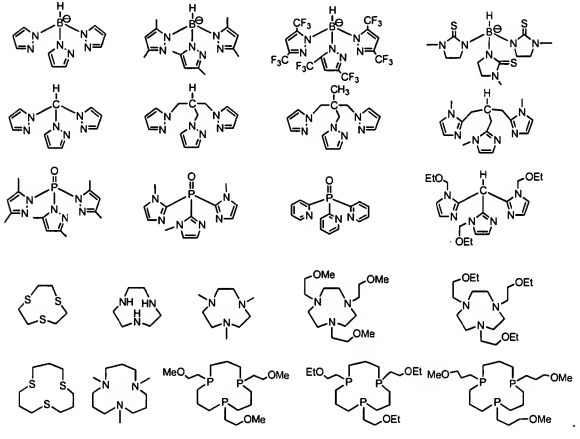
a is 2;

c is 2;

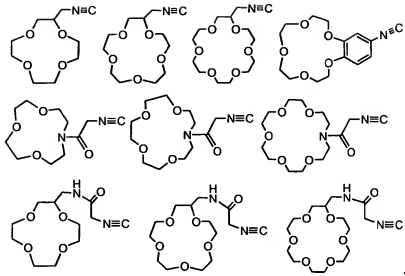
R^3, R^4 and R^5 can be the same or different, and are selected from: H, C_1-C_5 alkyl, phenyl, and macrocyclic crown ether containing 3 – 6 ether-oxygen atoms;

R^7, R^8 and R^9 can be the same or different, and are selected from: H, alkyl, and phenyl, or R^8 and R^9 may be taken together to form a macrocyclic crown ether containing 3 – 6 ether-oxygen atoms; and

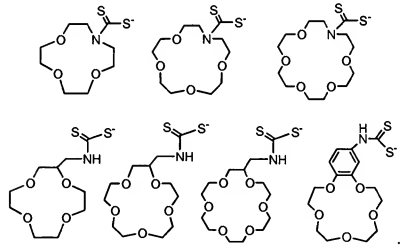
L^3, L^4 and L^5 are taken together to form a tripodal chelator of the formula:



[32] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [31], wherein L^3, L^4 and L^5 are the same and are selected from any one of following macrocyclic crown ether-containing isonitriles:



[33] Another more preferred embodiment of the present invention is a radiopharmaceutical of embodiment [31], wherein dithiocarbamate chelator is selected from any one of the following crowned DTCs:



[34] Another preferred embodiment of the present invention is a novel radiopharmaceutical composition containing a metal chelate according to embodiments [29] – [33].

[35] Another preferred embodiment of the present invention is a method for preparation of a radiopharmaceutical product according to embodiments [29] – [33], comprising reacting pertechnetate with (1) a nitrido donor; (2) a reducing agent; (3) an organic isonitrile ligand or tripodal chelator according to embodiments [29] – [33], and a crowned DTC chelator according to embodiments [1] – [9].

[36] Another preferred embodiment of the present invention is a method according to embodiment [35], wherein the nitrido donor is succinyl dihydride, and the reducing agent is stannous chloride.

[37] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiments [29] – [33], comprising:

a first bottle containing a nitrido donor, a stannous chloride and a chelating agent able to stabilize the tin cation,

a second bottle containing an organic isonitrile ligand or a tripodal chelator according to embodiments [29] – [33] and

a third bottle containing a crowned DTC chelator according to embodiments [1] – [9].

[38] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiment [37], comprising:

a first bottle containing a succinyl dihydride, a stannous chloride and 1,2-diaminopropane-N,N,N',N'-tetraacetic acid or a salt thereof, and

a second bottle containing an organic isonitrile ligand or a tripodal chelator according to embodiments [29] – [33], and a crowned DTC chelator according to embodiments [1] – [9].

[39] Another preferred embodiment of the present invention is a kit for preparation of a radiopharmaceutical product according to embodiment [36], comprising:

a first bottle containing a succinyl dihydride, a stannous chloride and 1,2-diaminopropane-N,N,N',N'-tetraacetic acid or a salt thereof, and

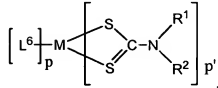
a second bottle containing an organic isonitrile ligand according to embodiments [29] – [33], and a crowned DTC chelator according to embodiments [4] – [9].

[40] Another preferred embodiment of the present invention is a novel radiopharmaceutical for radioimaging a mammal comprising (i) administering to said mammal an effective amount of a radiopharmaceutical according to embodiments [29] – [33], and (ii) scanning the mammal using a radioimaging device.

[41] In another preferred embodiment, the present invention provides a novel method for visualizing sites of myocardial disease in a mammal by radioimaging, comprising (i) administering to said mammal an effective amount of a radiopharmaceutical of formula according to embodiments [29] – [33], and (ii) scanning the mammal using a radioimaging device.

[42] In another preferred embodiment, the present invention provides a novel method of diagnosing a myocardial disease in a mammal comprising administering to said mammal a radiopharmaceutical composition of formula according to embodiments [29] – [33], and imaging said mammal.

[43] In a fourth embodiment, the present invention provides a novel pharmaceutical of the formula:



and pharmaceutically acceptable salt thereof, wherein

M is a transition metal selected from: Fe(II), Fe(III), Mn(II), Mn(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ru(II), Ru(III), Pd(II), and Pt(II);

p and p' are integers and are independently selected from 0 – 2;

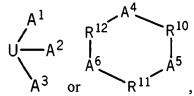
R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein

a is 2 – 5;

b is 3 – 8;

c is 2 – 5.

L^6 is a tripodal chelator to complete the coordination sphere of the transition metal, and is selected from a compound of the formula:



wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O);

A^1, A^2 and A^3 can be the same or different, and are imine-N containing heterocycles;

A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S;

R^{10}, R^{11} and R^{12} can be the same or different, and are selected from a group of the formula:

$$\text{-}(CH_2)_g\text{-},$$

wherein g is 2 – 5;

R^{13} is selected from: H, alkyl and aryl group; and

R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl;

[44] A preferred embodiment of the present invention provides a novel pharmaceutical according to embodiment [43], wherein M is Ru(III);

p is 1;

p'is 2;

R^1 and R^2 can be the same or different, and are selected from macrocyclic crown ether-containing group, or R^1 and R^2 may be taken together to form a macrocycle of the formula $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein

a is 2 or 3;

b is 3 – 6;

c is 2 or 3.

A^1, A^2 and A^3 are selected from a group: imidazoly, pyrazoly, oxazolinyl, methimazolyl, and pyridyl;

A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S;

g is 2 or 3;

R^{13} is selected from: H, methyl, and phenyl; and

R^{14} is ethyloxyethyl, ethoxylpropyl, methyoxyethyl, and methoxypropyl; and

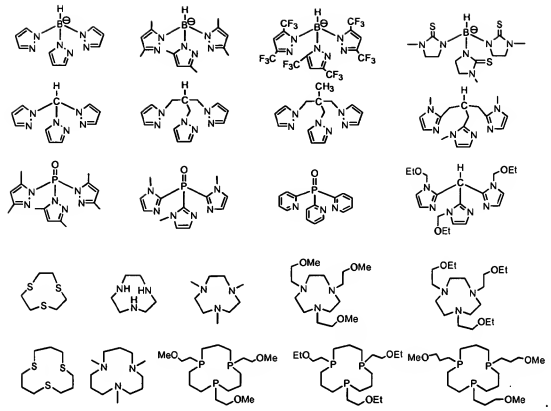
R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl;

[45] A more preferred embodiment of the present invention is a pharmaceutical of embodiment [44], wherein:

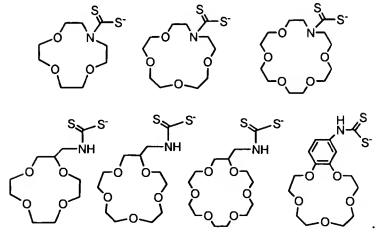
a is 2;

c is 2;

L^6 is selected from any one of the following tripodal chelator of the formula:



[46] Another more preferred embodiment of the present invention is a pharmaceutical of embodiment [45], wherein dithiocarbamate chelator is selected from any one of the following crowned DTCs:



II. Diagnostic and Therapeutic Uses

The crowned dithiocarbamate metal complexes of the present invention are preferably used as pharmaceutical agents to diagnose or treat disease.

A. Radiopharmaceutical Compositions

In certain embodiments, the crowned dithiocarbamate metal complexes of the present invention are neutral and cationic radioactive metal-nitrido complexes of crowned dithiocarbamates and are used as radiopharmaceuticals. Radiopharmaceuticals are drugs containing a radionuclide, and are used routinely in nuclear medicine department for the diagnosis or therapy of various diseases. They are mostly small organic or inorganic compounds with definite composition. Radiopharmaceuticals form the chemical basis for nuclear medicine, a group of techniques used for diagnosis and therapy of various diseases. The in vivo diagnostic information is obtained by intravenous injection of the radiopharmaceutical and determining its biodistribution using a gamma camera. The biodistribution of the radiopharmaceutical depends on the physical and chemical properties of the radiopharmaceutical and can be used to obtain information about the presence, progression, and the state of disease. The radioactive metal-nitrido complexes of crowned dithiocarbamates of the present invention are preferably used as radiopharmaceuticals.

The radionuclide for a diagnostic radiopharmaceutical is often a gamma-emitting isotope for scintigraphic imaging or positron-emitting isotope for positron emission tomography (PET). The choice of the radionuclide depends largely on the physical and nuclear properties (half-life and γ-energy), availability, and cost. Nearly 80% of all radiopharmaceuticals used in nuclear medicine department are ^{99m}Tc-labeled compounds. The 6 h half-life is long enough to allow a radiochemist to carry out radiopharmaceutical synthesis and for nuclear medicine practitioners to collect useful images. At the same time, it is short enough to permit the administration of millicurie amounts of ^{99m}Tc radioactivity without significant radiation dose to the patient. The monochromatic 140 KeV photons are readily collimated to give images of superior spatial resolution. Furthermore, ^{99m}Tc is readily available from commercial ^{99}Mo-^{99m}Tc generators at low cost.

In preferred embodiments, the metallic radionuclide is selected from the group: ^{99m}Tc, ^{186}Re and ^{188}Re. For diagnostic purposes ^{99m}Tc is the preferred isotope. Its 6 hour half-life and 140 keV gamma ray emission energy are almost ideal for gamma scintigraphy using equipment and procedures well established for those skilled in the art. The rhenium isotopes

also have gamma ray emission energies that are compatible with gamma scintigraphy, however, they also emit high energy beta particles that are more damaging to living tissues. These beta particle emissions can be utilized for therapeutic purposes, for example, cancer radiotherapy. The related chemistry, medical applications, and radiolabeling with $^{186/188}$Re by direct and indirect methods have been reviewed (Fritzberg, et al. *Pharmaceutical Res.* 1988, *5*, 325; Liu et al. *Bioconjugate Chem.* 1997, *8*, 621; Dilworth, J. R. and Parrott, S. J. *Chem. Soc. Rev.* 1998, *27*, 43).

^{99m}Tc is produced from a parent radionuclide, ^{99}Mo, a fission product with a half-life of 2.78 days. In a ^{99}Mo-^{99m}Tc generator, [^{99}Mo]molybdate is absorbed to an alumina column and ^{99m}Tc is formed by decay of ^{99}Mo. The ^{99m}Tc in the form of [^{99m}Tc]pertechnetate is eluted from the column with saline. The ^{99m}Tc produced by the generator is never carrier-free because fifteen percent of ^{99}Mo decays directly to the long-lived isotope ^{99}Tc ($t_{1/2}$ = 2.13 x 10^5 y), which is also the single decay product of ^{99m}Tc. The specific activity of eluted ^{99m}Tc is very high and is dependent upon the prior-elution time. In general, the total concentration of technetium (^{99m}Tc and ^{99m}Tc) in the ^{99}Mo-^{99m}Tc generator eluent is in the range of 10^{-7} – 10^{-6} M.

For the last two decades, PET imaging was only used for academic research, most likely due the short half-life of isotopes, availability of generator systems, practicality of isotope production, transportation and distribution of the radiotracer. The development of outside vendors who can supply PET isotopes to a number of local customers on a unit dose basis and the adaptability of SPECT cameras for PET imaging should increase the use of this imaging modality (Phelps, M. E. *J. Nucl. Med.* 2000, *41*, 661; Bar-Shalom et al. *Seminars Nucl. Med.* 2000, *30*, 150; and O'Doherty, M. J. *Nucl. Med. Commun.* 2000, *21*, 224, all of which are herein incorporated by reference). In certain embodiments, detection of the of the present invention are performed by PET imaging (e.g. using a SPECT camera or similar type camera).

Compared to other imaging modalities, PET has the following three important technological features, which enables clinicians to measure biochemical or physiological process in vivo. The first feature of PET is its ability to accurately measure the actual 3-D radiotracer distribution, which makes PET similar to autoradiography. The second feature is its ability to rapidly acquire a dynamic set of tomographic images through a volume of tissue. This is unique for PET imaging because no other imaging modality except MRI. The third feature of PET is the ability to acquire whole body images. It is the combination of these

three features with the high specificity of receptor binding of biomolecules that makes PET imaging using radiolabeled biomolecules extremely attractive for nuclear medicine. ^{94m}Tc is a cyclotron-produced isotope with a half-life of 52 min (0.9 h) and a β^+ energy of 2.47 MeV (72%). It can be obtained from a number of production methods, including ^{94}Mo(p, n)/^{94m}Tc (13.5 – 11 MeV), ^{nat}Nb(^{3}He, 2n)/^{94m}Tc (18 – 10 MeV), ^{92}Mo(α , pn)/^{94m}Tc (26 – 18 MeV). The quantitative superiority of PET permits modeling of radiotracer kinetics and dosimetry measurements. The successful preparation of ^{94m}Tc in the pertechnetate form allows the use of the same commercially available kit for ^{99m}Tc radiopharmaceuticals to prepare the ^{94m}Tc analogs. The use of dual isotopes ^{99m}Tc/^{94m}Tc (SPECT/PET) may provide much better imaging quality of diseased tissue. The integration of PET and SPECT radiotracer development would pave the way for better exploitation of the current strengths of the two imaging modalities, and will be extremely important for both the oncology and cardiology applications of radiopharmaceuticals such as ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosamin. As such, the use of both ^{99m}Tc/^{94m}Tc in the radioactive metal-nitrido complexes of crowned dithiocarbamates of the present invention in preferred in certain embodiments.

Rhenium shares the similar coordination chemistry with technetium due to their periodic relationship. Rhenium has two isotopes (^{186}Re and ^{188}Re) that are useful for radiotherapy. ^{186}Re has a half-life of 3.68 days with a $\tilde{\beta}$ emission (Emax = 1.07 MeV, 91% abundance) and a gamma-photon (E = 137 keV, 9% abundance) which should allow imaging during therapy. ^{186}Re is a reactor-produced radionuclide, and is obtained by the irradiation of ^{185}Re with neutrons (^{185}Re(n, γ)^{186}Re). The yield of ^{186}Re depends on the amount of Re target, the energy of the neutrons available, and the neutron reflux. The specific activity is low or medium, but a carrier-free product is not possible. As such, in certain embodiments, the radioactive metal-nitrido complexes of crowned dithiocarbamates of the present invention employ ^{186}Re and ^{188}Re as the radioactive metal.

^{188}Re has a half-life of 16.98 h with a high-energy β-emission (Emax = 2.12 MeV, 85% abundance) and 155 keV gamma photons (15% abundance). ^{188}Re can be prepared either from the nuclear reaction (^{187}Re(n, γ)^{188}Re) or from the ^{188}W-^{186}Re generator. The generator-produced ^{188}Re is carrier-free and has very high specific activity. The major advantage of using ^{188}Re in therapeutic nuclear medicine is the inexpensive and readily available ^{188}W-^{186}Re generator, which has a very long useful shelf-life.

There are many Tc cores for routine synthesis of ^{99m}Tc radiopharmaceuticals. The $[Tc=O]^{3+}$ core is stable in the presence of a strong chelator in aqueous media. It is the most frequently used Tc core for ^{99m}Tc radiopharmaceuticals. The $[Tc=O]^{3+}$ core forms square pyramidal Tc-oxo chelates with tetradentate chelators, including N_4 propylene amine oxime (PnAO), N_3S triamidethiols, N_2S_2 diamidedithiols (DADS), N_2S_2 monoamidemonoaminedithiols (MAMA), and N_2S_2 diaminedithiols (DADT). The $[Tc\equiv N]^{2+}$ core is isoelectronic with the $[Tc=O]^{3+}$ core. The nitrido ligand is a powerful π -electron donor and shows a high capacity to stabilize the Tc(V) oxidation state. The $[Tc\equiv N]^{2+}$ core forms Tc(V) nitrido complexes with a variety of chelators. Various chelators have been used for preparation of ^{99m}Tc radiopharmaceuticals. ^{99m}Tc-labeling techniques have been extensively reviewed (See, e.g., Hom, R. K. and Katzenellenbogen, J. A. *Nucl. Med. Biol.* 1997, *24*, 485; Dewanjee, M. K. *Semin. Nucl. Med.* 1990, *20*, 5; and Jurisson, et al *Chem. Rev.* 1993, *93*, 1137, all of which are herein incorporated by reference).

PCT application WO 90/06137 (herein incorporated by reference) disclosed a series of technetium-nitrido chelates of dithiocarbamates, including dimethyldithiocarbamate, di-n-propyl dithiocarbamate, N-ethyl-N-(2-ethyoxyethyl)dithiocarbamate. PCT applications (WO 89/08657, WO 92/00982, and WO 93/01839, herein incorporated by reference) disclose processes for producing a technetium nitrido complexes, which comprises reacting a polyphosphine as a reducing agent for the technetium oxide, then reacting with a nitride salt of a metal or ammonium ion. Since Tc-nitrido core has four to five coordination sites for various ligands or chelators, the choice of chelator is important for the solution stability and number of radioactive species form during ligand exchange reaction.

US patents (5,288,476 and 6,071,492, both of which are herein incorporated by reference) disclosed cardiac tropism radiopharmaceutical products incorporating a nitride complex of transition metal and having a rapid myocardial clearance. Substituents on the dithiocarbamate-N atoms are selected from a branched alkyl group having one or more ether functions, a tetrahydrofurfuryl or ether group, a tetrahydrofurfuryl or dioxaspiro or dialyoxy piperidino groups. Because of these ether-containing groups, the ^{99m}Tc complexes of dithiocarbamate show rapid clearance from the liver and lungs, resulting high heart/liver and heart/lung ratios. These references do not teach the formation of macrocyclic crown ether from the two substituents on the dithiocarbamate-N atom, nor the use of crowned DTCs for preparation of ^{99m}Tc-nitrido complexes as described in this invention.

PCT application WO98/27100 (herein incorporated by reference) discloses ^{99m}Tc chelate radiopharmaceuticals comprising ^{99m}Tc-nitrido and two different bidentate ligands coordinated therewith. Although the bisphosphine was originally proposed as a bidentate chelator; but structural studies have clearly demonstrated that the bisphosphine chelator is actually tridentate to form the six-coordinate Tc-nitrido complex with a bidentate chelator such as dithiocarbamate as coligand.

PCT application WO02/09771 (herein incorporated by references) discloses a new class of asymmetric cationic ^{99m}Tc-nitrido complexes, which contain a $[^{99m}Tc{\equiv}N]^{2+}$ core, a tridentate PXP bisphosphine, and a DTC chelator. It was found that these cationic ^{99m}Tc-nitrido complexes are rapidly extracted by the myocardium of rats, and retained in the heart for a long time. The lung uptake became negligible at 5 min postinjection, and liver washout was also very fast. Substituents on the phosphine-P, secondary amine-N, and dithiocarbamate-N atoms are selected from alkyl, aryl, alkoxy, or alkoxyalkyl group. This reference does not disclose the use of crowned DTCs for preparation of ^{99m}Tc-nitrido complexes.

Ischemia-related diseases, particularly coronary artery disease (CAD), account for the majority of death in Western countries. Myocardial ischemia is a serious condition and the delay in reperfusion of the ischemic tissues can be life threatening. This is particular true in the aged population. Rapid and accurate early detection of myocardial ischemia is highly desirable so that various therapeutic regiments can be given before irreversible myocardial damage occurs. In this regard, the compositions of the present invention are preferably used for myocardial perfusion imaging.

Myocardial perfusion imaging with radiotracers is an integral component of the clinical evaluation of patients with known or suspected coronary artery disease (CAD) in current clinical practice (See, e.g., Acmpa, W., et al *J. Nucl. Cardiol.* 2000, 7, 701; Berman, D., et al *Semin. Nucl. Med.* 1999, 29, 280; and Dilsizian, V. *J. Nucl. Cardiol.* 2000, 7, 180, all of which are herein incorporated by reference). The introduction of thallium-201 (^{201}Tl) in the mid 1970s was the turning point in the widespread clinical use of myocardial perfusion imaging, and had a profound impact on diagnostic evaluation, risk stratification, and therapeutic decision-making in patients with CAD over the last two decades. However, ^{201}Tl has its limitations. The vulnerability of ^{201}Tl to attenuation artifacts caused by the relatively lower energy emitted photons and lower count rate caused by the dose constraints may results in poor or suboptimal images in a significant proportion of studies. In addition, ^{201}Tl

images should be taken soon after injection, and may not be suitable for situations where immediate imaging may not be possible (for example, patients with acute myocardial infarction), mainly due to the dynamic nature of its distribution and redistribution dynamics. Compared to ^{201}Tl, ^{99m}Tc yields relatively high-energy photons and can be used at much higher doses. The use of ^{99m}Tc also allows the simultaneous assessment of myocardial perfusion and cardiac function in a single study (Kapur, A. et al *Eur. J. Nucl. Med.* 2002, 29, 1608, herein incorporated by reference). Because of its ideal nuclear properties (short half-life and γ-energy) and its diverse coordination chemistry, ^{99m}Tc has been the isotope of choice for the development of myocardial perfusion imaging agents.

^{99m}TcN-Noet is a member of neutral ^{99m}Tc-nitrido complexes, which are characterized by the presence of the $^{99m}Tc{\equiv}N$ triple bond and two N-alkyl dithiocarbamate ligands. Duatti and coworkers first reported the synthesis of ^{99m}Tc-nitrido complexes with various chelators and their use as heart imaging agents (Marchi, A. et al *J. Chem. Soc. Dalton Trans.* 1990, 1743; Duatti, A., et al *J. Chem. Soc., Dalton Trans.* 1990, 3729; Marchi, A et al *Inorg. Chem.* 1990, 29, 2091; herein incorporated by reference). Biodistribution studies demonstrated that these neutral ^{99m}Tc-nitrido complexes localized in the myocardium of rats, dogs, and primates. The high quality of myocardial images obtained in dogs and monkeys demonstrates that ^{99m}TcN-Noet has the most favorable distribution properties. ^{99m}TcN-Noet is currently in phase III clinical trials in Europe.

One aspect of this invention relates to neutral ^{99m}Tc-nitrido complexes as new radiopharmaceuticals for myocardial imaging. The ^{99m}Tc-nitrido complexes described in this invention are expected to have the first-pass extraction comparable to or better than that of ^{99m}Tc-N-Noet due to their structural similarity. The presence of crown ether group in the compounds of the present invention should allow a faster clearance of ^{99m}Tc-nitrido complexes from the liver and lungs, and better heart/liver and heart/lung ratios.

Another aspect of this invention relates to cationic ^{99m}Tc-nitrido complexes containing two different chelators, one of which is a crowned DTC, and their use as new radiopharmaceuticals for imaging (e.g. myocardial perfusion imaging). These cationic ^{99m}Tc-nitrido complexes are expected to have a higher heart uptake and longer myocardial retention than that of ^{99m}Tc-N-Noet due to the cationic character and possible interactions between crown ether moiety and intracellular K^+. The presence of crown ether groups also result in a faster renal clearance with less hepatobiliary uptake and gastrointestinal retention

than that of ^{99m}Tc-N-Noet, ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin due to the increased hydrophilicity.

Zhang and coworkers recently also reported the use of neutral ^{99m}Tc-nitrido complexes as brain imaging agents (Zhang, J. et al *Nucl. Med. Biol.* 2002, 29, 665; Zhang, J., et al *Appl. Radiat. Isot.* 2002, 56, 857; Zhang, Jet al *Appl. Radiat. Isot.* 2001, 54, 745; and Zhang, J. and Wang, X. *Appl. Radiat. Isot.* 2001, 55, 453). In these complexes, substituents on the dithiocarbamate-N atom are simple alkyl or cycloalkyl groups. Compared to cationic agents, the clearance of ^{99m}TcN-Noet from blood is significantly slower. ^{99m}TcN-Noet also shows high initial pulmonary uptake and prolonged liver retention. The combination of slow blood clearance and pulmonary uptake imposes a significant challenge for optimal myocardial perfusion imaging. In contrast in some embodiments, the composition of the present invention have high uptake in the heart and reduced liver retention.

Recently, Duatti and coworkers (Boschi, A. et al *Nucl. Med. Commun.* 2002, 23, 689; Bolzati, C. et al *J. Am. Chem. Soc.* 2002, 124, 11468) reported a new class of asymmetric cationic ^{99m}Tc-nitrido complexes, which contain a $[^{99m}Tc{\equiv}N]^{2+}$ core, a tridentate PXP bisphosphine, and a DTC chelator, and their biological evaluation as radiopharmaceuticals for heart imaging. It was found that these cationic ^{99m}Tc-nitrido complexes are rapidly extracted by the myocardium of rats, and retained in the heart for a long time. The lung uptake became negligible at 5 min postinjection, and liver washout was also very fast. Heart/liver ratios were increased exponentially with time, and the liver activity was almost completely eliminated into the intestine at 60 min postinjection. The heart/liver ratios were ~10 times higher than those of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin in the same animal model.

It should be noted that the heart uptake of lipophilic cations is not just limited to ^{99m}Tc complexes. It has been reported that cationic ^{64}Cu complexes show high heart uptake (Packard, A. B. *Nucl. Med. Biol.* 1998, 25, 531; Packard, A. B. *Nucl. Med. Biol.* 2002, 29, 289). Lipophilic ^{68}Ga complex cations have also been found to show a high heart uptake and are useful for evaluation of myocardial perfusion using PET (Tsang, B. W. et al *J. Nucl. Med.* 1993, 34: 1127; Tsang, B. W. et al *J. Med. Chem.* 1994, 37, 4400). It has also been demonstrated that the 3-methoxy or 3-ethoxy group is very important for high heart uptake for ^{68}Ga chelates. Studies on Q-series of cationic ^{99m}Tc complexes also showed that pendent ether moieties from phosphine ligands could improve the myocardial imaging properties

(Lisic, E. C. et al *Nucl. Med. Biol.* 1999, 26, 563; Marmion, M. E. et al *Nucl. Med. Biol.* 1999, 26, 755).

In addition to the cardiology applications, the radioactive metal-nitrido complexes of crowned dithiocarbamates of the present invention (e.g., ^{99m}Tc complexes) may also be used as radiopharmaceuticals for non-invasive imaging any type of tissue, including tumor MDR1 (multidrug resistance) p-glycoprotein (Pgp) transport function (Sharma, V. and Piwnica-Worms, D. *Chem. Rev.* 1999, 99: 2545; and Herman, L.et al., D. *J. Med. Chem.* 1995, 38: 2955). Various cationic ^{99m}Tc complex radiopharmaceuticals, originally developed for myocardial perfusion imaging, have been shown to be substrates for transport by MDR1 Pgp.

A crown ether containing dithiodicarbamate and its Co(II), Ni(II), Cu(II) and Zn(II) complexes have been synthesized and characterized (Wang,J. H. and Wang, Y. L. *Yingyong Huaxue* 2002, 19, 295-297; Wang, J.-H. and Zhang, Z. *Yingyong Huaxue* 1994, 11, 101). It was found that all metal complexes were stable, and the dithiocarbamate group is bidentate. The crystal structure of cobalt tris[(aza-15-crwon-5)dithiocarbamate has also been reported (Granell, G. et al *J. Chem. Soc., Dalton Trans.* 1990, 605); but no specific applications were disclosed.

B. Additional Therapeutic Uses

The compounds of the present invention, besides their use as radioimaging agents, may also be used to treat disease. The enhanced profile of metal in medicine in recent years cascades from the ongoing search for new therapeutic agents with unique mechanisms of action (Abrams, M. J. and Orvig, C. *Chem. Rev.* 1999, *99*, 2201; Thompson, K. H. and Orvig, C. Science 2003, *300*, 936; Clarke, M. J. *Coord. Chem. Rev.* 2002, *232*, 69-93). The therapeutic uses of ruthenium complexes, in particular, are of interest and have been investigated as immunosuppressive agents (Bastos, C. M. et al *Bioorg. Med. Chem. Lett.* 1998, *8*, 147), antitumor and anti-metastatic agents (Sava, G. et al *Top. Biol. Inorg. Chem.* 1999, *1*, 143; Sava, G. et al *Chem.-Biol. Interact.* 1995, *95*, 109; Sava, G. et al *Top. Biol. Met.-Based Drugs* 1995, *2*, 221), and nitric oxide (NO) scavengers (Cameron, B. R. *Inorg. Chem.* 2003, *42*, 4102; Chatterjiee, D. et al *Dalton Trans.* 2003, 203). The overproduction of NO has been implicated to play a significant role in many disease states such as septic shock (Evans, T. et al *Circ. Schock* 1993, *41*, 77), rheumatoid arthritis (Wei, et al *Nature* 1995, *375*, 408; Stefanovic-Racic, M. et al *Arthritis Rheum.* 1993, *36*, 1036), diabetes (Corbett, J. A. and McDaniel, M. L. *Diabetes* 1992, *41*, 849), asthma (Hamid, Q et al *Lancet*

1993, *342*, 1510), and cancer (Gallo, O. et al *J. Natl. Cancer Inst.* 1998, *90*, 587). Therefore, in certain embodiments, Ru(III) metal complexes pharmaceuticals of the present invention would be beneficial for the treatment of diseases such as septic shock, rheumatoid arthritis, diabetes, asthma, and cancer.

Dithiocarbamates (DTCs) are known heavy metal chelators (Sunderman, F. W. *Ann. Clin. Lab. Sci.* 1978, 8: 259; Jones, M. M. and Cherian, M. G. *Toxicology* 1990, 62: 1). DTCs such as diethyl-dithiocarbamate have been clinically used for the treatment of nickel poisoning, and were used in clinical trials for the treatment of AIDS patients (Reisinger, E., et al. *Lancet* 1990, 335: 679). DTCs such as pyrrolidine dithiocarbamate are potentent inhibitors of nuclear factor kappa B in intact cells (Schreck, R. et al. *J. Exp. Med.* 1992, 175: 1181). In addition, nuclear factor kappa B has been shown to up-regulate the expression of cell adhesive molecules, including the vascular cell adhesive molecule 1 (VCAM-1) (Iademarco et al. *J. Biol. Chem.* 1992, 267: 16323). Endothelial expression of VCAM-1 causes the adherence of neutrophils to the endothelium, an early event leading to inflammation and subsequent vascular damage and reduction of blood flow (Oppenheimer, M. N. et al. *J. Immunol.* 1991, 147: 42207). Therefore, DTCs and their metal complexes would block VCAM-1 expression, thereby avoiding the vascular problems associated with neutrophil adherence to the endothelium.

PCT application WO 01/62085 A1 discloses conjugates of dithiocarbamates and pharmacologically active agents for the treatment of inflammatory diseases. US patent application (US 2002/0045573 A1) also disclosed DTC-containing drugs for therapeutic treatment of such indications as cerebral stroke and other ischemia/reperfusion injury. In these disclosed agents, the DTC moiety is linked to the surface of a non-immunogenic, non-targeting macromolecule other than an antibody. The metal chelates of a composition comprising a DTC and a non-immunogenic, non-targeting macromolecule can also be used for the same purpose (US 2002/0045573 A1). Recent studies have shown that DTC chelators act either as a direct scavenger of hydroxy radicals (due to its thiol group) or as iron chelator that inhibit hydroxyl radical production by binding to the iron ions or by both mechanisms (Liu, et al. *Free Rad. Res.* 1996, 24: 461).

Another aspect of this invention relates to compositions of the present invention (e.g. neutral or cationic metal chelates) as niric oxide (NO) scavengers. The presence of crown ether groups may be used to increase water solubility. Metal chelate-based NO scavengers

are useful as therapeutic pharmaceuticals would for the treatment of diseases including, but not limited to, septic shock, rheumatoid arthritis, diabetes, asthma, and cancer.

In the last decade, nitric oxide has been widely studied because of its essential role in many physiological processes. The overproduction of NO has been implicated to play a significant role in many disease states such as septic shock (Evans, T. et al *Circ. Schock* 1993, *41*, 77), rheumatoid arthritis (Wei, et al *Nature* 1995, *375*, 408; Stefanovic-Racic, M. et al *Arthritis Rheum.* 1993, *36*, 1036), diabetes (Corbett, J. A. and McDaniel, M. L. *Diabetes* 1992, *41*, 849), asthma (Hamid, Q et al *Lancet* 1993, *342*, 1510), and cancer (Gallo, O. et al *J. Natl. Cancer Inst.* 1998, *90*, 587). Therefore, the compositions of the present invention may be used, based on their NO attenuation or scavenging properties, as compounds for the treatment of diseases such as septic shock, rheumatoid arthritis, diabetes, asthma, and cancer.

Nitric oxide is an excellent ligand, especially with iron and ruthenium. Iron complexes of dithiocarbamates have been used as NO scavengers (Fujii, S. et al. *Chem. Lett.* 1996, 785). More recently, Cu(II) complexes of dithiocarbamates have also be studied as NO scavengers (Diaz, A. et al. *J. Inorg. Biochem.* 2003, 95: 283). It was found that the complex $Cu(ProDTC)_2$ (ProDTC = L-prolinedithiocarbamate) has a extremely high binding affinity for NO: $\log \beta_1 = 9.74$ and $\log \beta_2 = 15.44$. Ruthenium(III) complexes are of particular interest as NO scavengers, and have been investigated as immunosuppressive agents (Bastos, C. M. et al *Bioorg. Med. Chem. Lett.* 1998, *8*, 147), antitumor and anti-metastatic agents (Sava, G. et al *Top. Biol. Inorg. Chem.* 1999, *1*, 143; Sava, G. et al *Chem.-Biol. Interact.* 1995, *95*, 109; Sava, G. et al *Top. Biol. Met.-Based Drugs* 1995, *2*, 221), and nitric oxide (NO) scavengers (Cameron, B. R. *Inorg. Chem.* 2003, *42*, 4102; Chatterjiee, D. et al *Dalton Trans.* 2003, 203). Another aspect of this invention provides the use of the compounds of the present invention as sequestering agents for the treatment of heavy metal (e.g., Fe^{3+} and Pb^{2+}) intoxication.

III. Methods of Making Crowned Dithiocarbamate Metal Complexes

Methods of making the crowned dithiocarbamate metal complexes of the present invention are described in the Examples below. Variations of these methods may also be employed. Additional details for making the compositions of the present invention are provided below.

Dithiocarbamates are sulfur-containing small molecules with extremely useful redox capability. DTCs have been used as heavy metal chelators. Synthesis of crowned DTC

chelators was achieved by reacting the amino crown ether with carbon disulfide in the presence of a base such as sodium hydroxide (Wang,J. H. and Wang, Y. L. *Yingyong Huaxue* 2002, 19, 295-297; and Wang, J.-H. and Zhang, Z. *Yingyong Huaxue* 1994, 11, 101; all of which are herein incorporated by reference). Since these crowned DTCs are slightly air-sensitive, they should be dried and stored under nitrogen. The size and the number of ether-oxygen donors can be systematically varied using synthetic techniques known in the prior art.

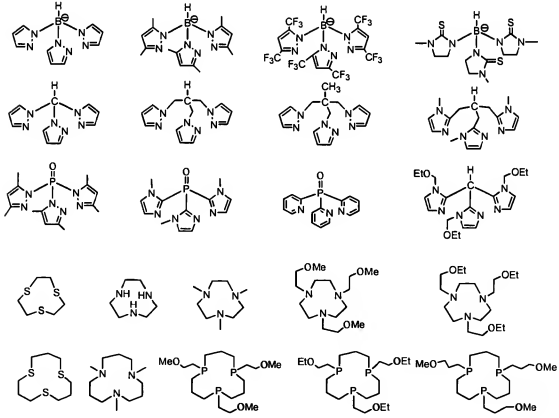
DTC chelators form metal complexes with a variety of transition metal ions, including Fe^{2+}, Fe^{3+}, Co^{2+}, Co^{3+}, Cu^{2+}, Mn^{2+}, Zn^{2+}, and Ru^{3+}. It has been well-documented that DTC chelators form neutral ^{99m}Tc-nitrido complexes. Synthesis of neutral ^{99m}Tc-nitrido complexes of crowned DTCs can be achieved by following the literature methods (Marchi, A. et al *J. Chem. Soc. Dalton Trans.* 1990, 1743; Duatti, A., et al *J. Chem. Soc., Dalton Trans.* 1990, 3729; Pasqualini, R. et al *Appl. Radiat. Isot.* 1992, 43: 1329; Pasqualini, R.et al *J. Nucl. Med.* 1994, 35: 334; Zhang, J. et al *Nucl. Med. Biol.* 2002, 29, 665; Zhang, J., et al *Appl. Radiat. Isot.* 2002, 56, 857; Zhang, Jet al *Appl. Radiat. Isot.* 2001, 54, 745; Zhang, J. and Wang, X. *Appl. Radiat. Isot.* 2001, 55, 453; all of which are herein incorporated by reference).

Macrocyclic crown ethers containing groups have been the subject of intensive research for their capability to bind metal ion such as K^+ and Na^+ (Valeur, B., and Leray, I. *Coord. Chem. Rev.* 2000, 205: 3; Gunnlaugsson, T., and Leonard, J. P. *J. Chem. Soc., Perkin Trans.* 2002, 2: 1980). The extracellular Na^+ concentration is 133 – 145 mM as compared to 3.5 – 4.8 mM for K^+. However, the cytosolic Na^+ concentration is only 10 – 40 mM as compared to 120 mM (upper limit) for K^+ (Gunnlaugsson, T., and Leonard, J. P. *J. Chem. Soc., Perkin Trans.* 2002, 2: 1980; Gunnlaugsson, T. et al. *J. Chem. Soc., Perkin Trans.* 2002, 1: 1954). Although the 12- and 15-membered crown ether may not be able to form stable K^+ complexes, the 18-membered crown ether group may result in a stronger interaction with K^+. Therefore, the K^+ binding capability may serve as a driving force for accumulation and retention of ^{99m}Tc complexes in myocardium. The selectivity for K^+ can be tuned by changing size and number of oxygen donor atoms of the macrocycle.

Recently, Duatti and coworkers (Boschi, A. et al *Nucl. Med. Commun.* 2002, 23, 689; Bolzati, C. et al *J. Am. Chem. Soc.* 2002, 124, 11468) reported a new class of asymmetric cationic ^{99m}Tc-nitrido complexes, which contain a $[^{99m}Tc{\equiv}N]^{2+}$ core, a tridentate PXP bisphosphine, and a DTC chelator, and their biological evaluation as radiopharmaceuticals for heart imaging. It was found that these cationic ^{99m}Tc-nitrido complexes are rapidly

extracted by the myocardium of rats, and retained in the heart for a long time. The lung uptake became negligible at 5 min postinjection, and liver washout was also very fast. Heart/liver ratios were increased exponentially with time, and the liver activity was almost completely eliminated into the intestine at 60 min postinjection. The heart/liver ratios were ~10 times higher than those of ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin in the same animal model.

Duatti and coworkers (Bolzati, C. et al *J. Am. Chem. Soc.* 2002, 124, 11468) have elegantly demonstrated that the heteroatom in the tridentate PXP (X = O and NR) ligand is required for stable asymmetrical ^{99m}Tc-nitrido complexes with the heteroatom invariably *trans* to the Tc≡N triple bond. The observed metal-heteroatom distances are quite long; but this weak interaction seems play a significant role in providing a further stabilization for the ^{99m}Tc-nitrido core. These findings support the idea of using other tridentate chelators as tridentate co-ligands for the preparation of the mixed-ligand cationic ^{99m}Tc-nitrido complexes. The tripodal chelators of particular interests include, but not limited to, the following examples:



Like phosphine-P, thioether-sulfurs are π -acceptors. Although the Tc-S interaction is not as strong as Tc-P (phosphine) bond, the macrocyclic effect will definitely enhance the stability

of the *fac*-[^{99m}TcN([9]aneS$_3$)]$^{2+}$ fragment. Imine-N containing heterocycles are π -acceptors. From this point of view, tridentate imine-N containing tropodal chelators should also be used to form highly stable *fac*-[^{99m}TcN(N$_3$)]$^{+/2+}$ fragments. The same basic idea should also apply to the fragment *fac*-[^{99m}TcN([9]aneN$_3$)]$^{2+}$ except that [9]aneN$_3$ is not be a π -acceptor. The exact structure of a particular radiometal complex described in the present invention will depend on the identity of the tripodal coligand. In most cases, the tripodal coligand will occupy three coordination sites, and only one crowned DTC chelator is needed to complete the octahedral coordination sphere of the radionuclide, such as ^{99m}Tc.

Zhang and coworkers (*J. Labeled Compounds and Radiopharmaceuticals* 2002, 45: 1029) reported synthesis of a ^{99m}Tc-nitrido complex [^{99m}TcNCl$_2$(MIBI)$_3$]. Radio-HPLC data revealed only one peak for the complex [^{99m}TcNCl$_2$(MIBI)$_3$]. Although the exact composition for [^{99m}TcNCl$_2$(MIBI)$_3$] is not known, electrophoresis data suggested that it is most likely neutral with three MIBI ligands and two chloride anions bonding to the Tc. It was also found that one of the two chloride ligands is very labile, which was attributed to the partial cationic characteristics for the complex [^{99m}TcNCl$_2$(MIBI)$_3$] in solution.

In order to prevent partial dissociation, a bidentate dithiocarbamate chelator can be used to replace the two chlorides and form cationic ^{99m}Tc-nitrido complexes [^{99m}TcN(Isonitrile)$_3$(L)]$^+$. The advantage of this new chelating system (three isonitriles and a dithiocarbamate) is the versatility of both isonitrile and dithiocarbamate ligands, which can be used for modification of physical and biological properties of their cationic ^{99m}Tc-nitrido complexes [^{99m}TcN(Isonitrile)$_3$(L)]$^+$. If one crown ether group in complexes [^{99m}TcN(isonitrile)$_3$(L)]$^+$ does not provide sufficient improvement in hydrophilicity, the combination of three crown ether-containing isonitriles with one crowned DTC will result in a significant improvement in lipophilicity of their cationic ^{99m}Tc-nitrido complexes.

The technetium and rhenium radionuclides are preferably in their chemical form of [^{99m}Tc]pertechnetate or [$^{186/188}$Re]perrhenate and a pharmaceutically acceptable cation. The [^{99m}Tc]pertechnetate salt form is preferably sodium [^{99m}Tc]pertechnetate such as obtained from commercial ^{99m}Tc generators. The amount of [^{99m}Tc]pertechnetate used to prepare the metal complexes of the present invention can range from 1 mCi to 1000 mCi, or more preferably from 1 mCi to 50 mCi. Since there is no effective chemistry that can be used to attach the [^{99m}Tc]pertechnetate anion to an organic chelator, the [^{99m}Tc]pertechnetate has to be reduced by a reducing agent to a lower oxidation state in order to produce a stable ^{99m}Tc complex or to a reactive intermediate complex from which ^{99m}Tc can be easily transferred to

the new chelator to form the expected ^{99m}Tc complex. The rhenium chemistry is very similar to technetium chemistry due to the periodic relationship. Therefore, the methods used for molecules labeled with ^{99m}Tc should apply to those labeled with $^{186/188}$Re.

Suitable reducing agents for the synthesis of radiopharmaceuticals of the present invention include stannous salts, dithionite or bisulfite salts, borohydride salts, and formamidinesulfinic acid, wherein the salts are of any pharmaceutically acceptable form. The preferred reducing agent is a stannous salt. The amount of a reducing agent used can range from 0.001 mg to 10 mg, or more preferably from 0.005 mg to 1 mg.

The total time of preparation will vary depending on the metallic radionuclide, the identities and amounts of the reactants and the procedure used for the preparation. The preparations may be complete, resulting in > 80% yield of the metal complex, in 1 minute or may require more time. After the radiolabeling, the resulting reaction mixture may optionally be purified using one or more chromatographic methods, such as Sep-Pack or high performance liquid chromatography (HPLC). The preferred methods are those, in which the ^{99m}Tc complex is prepared in high yield and high radiochemical purity without post-labeling purification.

The amounts of the DTC chelator used for preparation of radiometal chelates can range from, for example, 1 mg to 1000 mg, or more preferably from 1 mg to 10 mg. The exact amount of the DTC chelator is a function of the identity of a specific metal chelate, the procedure used for preparation of the metal chelate, and the amount and identities of the reactants used for the radiolabeling.

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

IV. Pharmaceutical Compositions and Kits Thereof

Described below are certain kits and therapeutic compositions, as well as various routes of therapeutically administering compositions of the present invention.

In certain embodiments, the present invention provides diagnostic kits for the preparation of radiopharmaceuticals useful as imaging agents for the diagnosis of cardiovascular disorders, infectious disease, inflammatory disease and cancer. Diagnostic kits of the present invention may comprise one or more vials containing the sterile, non-pyrogenic, formulation comprised of a predetermined amount of the chelator described in this invention, a stabilizing coligand, if needed, a reducing agent, and optionally other components such as buffers, lyophilization aids, stabilization aids, solubilization aids and bacteriostats.

A radiopharmaceutical composition may contain, for example, the metal complex radiopharmaceutical, a buffer, a stabilization aid to prevent autoradiolysis, and a bacteriostat. If radiopharmaceutical is prepared using the kit formulation, the radiopharmaceutical composition may contain the metal complex radiopharmaceutical and kit components, including unlabeled chelator, excess stabilizing coligand, a reducing agent, buffer, lyophilization aid, stabilization aid, solubilizing aids, and bacteriostats.

Buffers useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to phosphate, citrate, sulfosalicylate, and acetate. A more complete list can be found in the United States Pharmacopeia. Lyophilization aids useful in the preparation of diagnostic kits useful for the preparation of radiopharmaceuticals include but are not limited to mannitol, lactose, sorbitol, dextran, Ficoll, and polyvinylpyrrolidine (PVP).

Stabilization aids useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to ascorbic acid, cysteine, monothioglycerol, sodium bisulfite, sodium metabisulfite, gentisic acid, ascorbic acid, and inositol.

Solubilization aids useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to ethanol, glycerin, polyethylene glycol, propylene glycol, polyoxyethylene sorbitan monooleate, sorbitan monoloeate, polysorbates, poly(oxyethylene)poly(oxypropylene) poly(oxyethylene) block copolymers (Pluronics) and lecithin. Preferred solubilizing aids are polyethylene glycol, and Pluronics.

Bacteriostats useful in the preparation of radiopharmaceuticals and in diagnostic kits useful for the preparation of said radiopharmaceuticals include but are not limited to benzyl alcohol, benzalkonium chloride, chlorbutanol, and methyl, propyl or butyl paraben.

A component in a diagnostic kit can also serve more than one function. A reducing agent can also serve as a stabilization aid, a buffer can also serve as a transfer ligand, a lyophilization aid can also serve as a transfer, ancillary or coligand and so forth.

The predetermined amounts of each component in the formulation are determined by a variety of considerations that are in some cases specific for that component and in other cases dependent on the amount of another component or the presence and amount of an optional component. In general, the minimal amount of each component is used that will give the desired effect of the formulation. The desired effect of the formulation is that the practising end user can synthesize the radiopharmaceutical and have a high degree of certainty that the radiopharmaceutical can be safely injected into a patient and will provide diagnostic information about the disease state of that patient.

The diagnostic kits of the present invention may also contain written instructions for the practicing end user to follow to synthesize the radiopharmaceuticals. These instructions may be affixed to one or more of the vials or to the container in which the vial or vials are packaged for shipping or may be a separate insert, termed the package insert.

In some embodiments, the pharmaceutical compositions of the present invention comprise pharmaceutical carriers including, but not limited to, any sterile biocompatible pharmaceutical carrier such as saline, buffered saline, dextrose, water, and the like. Accordingly, in some embodiments, the methods of the present invention comprise administering to a subject a pharmaceutical composition of the present invention in a suitable pharmaceutical carrier. In some embodiments, particular pharmaceutical compositions or therapies comprise a mixture of two or more different species of pharmaceutical composition.

In still further embodiments, the pharmaceutical compositions comprise a plurality of compositions administered to a subject under one or more of the following conditions: at different periodicities, different durations, different concentrations, or by different administration routes and the like.

In some preferred embodiments, the pharmaceutical compositions and methods of the present invention find use in treating diseases or altered physiological states characterized by pathogenic infection. However, the present invention is not limited to ameliorating (*e.g.*, treating) any particular disease or infection. Indeed, various embodiments of the present invention are provided for treating (including prophylaxis) a range of physiological symptoms and disease etiologies in subjects including but limited to, those characterized by

aberrant cellular growth or proliferation (*e.g.*, cancer), autoimmunity (*e.g.*, rheumatoid arthritis), and other aberrant biochemical, genetic, and physiological symptoms. Depending on the condition being treated, the pharmaceutical compositions are formulated and administered systemically or locally. Techniques for pharmaceutical formulation and administration are generally found in the latest edition of "Remington's Pharmaceutical Sciences" (Mack Publishing Co, Easton Pa.). Accordingly, the present invention contemplates administration of the pharmaceutical compositions in accordance with acceptable pharmaceutical delivery methods and preparation techniques.

In some embodiments of the present invention, pharmaceutical compositions are administered to a subject (patient) alone or in combination with one or more other drugs or therapies (*e.g.,* antibiotics and antiviral agents, *etc*) or in compositions where they are mixed with excipients or other pharmaceutically acceptable carriers.

Generally, the pharmaceutical compositions of the present invention may be delivered via any suitable method, including, but not limited to, orally, intravenously, subcutaneously, intratumorally, intraperitoneally, or topically (*e.g.*, to mucosal surfaces).

In some preferred embodiments, the pharmaceutical compositions of the present invention are formulated for parenteral administration, including intravenous, subcutaneous, intramuscular, and intraperitoneal. Some of these embodiments comprise a pharmaceutically acceptable carrier such as physiological saline. For injection, the pharmaceutical compositions are typically formulated in aqueous solution, preferably in physiologically compatible buffers (*e.g.,* Hanks' solution, Ringer's solution, or physiologically buffered saline). For tissue or cellular administration, penetrants appropriate to the particular barrier to be permeated are also preferable. Such penetrants are well known in the art. Other embodiments use standard intracellular delivery (*e.g.,* delivery via liposomes) techniques. Intracellular delivery methods are well known in the art. Administration of some agents to a patient's bone marrow may necessitate delivery in a manner different from intravenous injections.

In other embodiments, active pharmaceutical compositions are prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injectable suspensions may additionally comprise substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Optionally, the injectable suspension may also comprise suitable stabilizers and agents that

increase or prolong the solubility of the compounds thus allowing preparation of highly concentrated solutions.

In other embodiments, the present pharmaceutical compositions are formulated using pharmaceutically acceptable carriers in suitable dosages for oral administration. Suitable carriers enable the compositions to be formulated as tablets, pills, capsules, dragees, liquids, gels, syrups, slurries, suspensions and the like, for oral or nasal ingestion by a subject. In some embodiments, pharmaceutical compositions for oral use are made by combining the active compounds (*e.g.*, chemical address tag-therapeutic agent conjugates) with a solid excipient, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, so as to obtain tablets or dragee cores. Suitable excipients include, but are not limited: carbohydrate fillers such as sugars, including, lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums including arabic and tragacanth; and proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as cross-linked polyvinyl pyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate.

Ingestible formulations of the present pharmaceutical compositions may further comprise any material approved by the United States Department of Agriculture (or other similar international agency) for inclusion in foodstuffs and substances that are generally recognized as safe (GRAS) such as, food additives, flavorings, colorings, vitamins, minerals, and phytonutrients. The term "phytonutrients" as used herein, refers to organic compounds isolated from plants that have a biological affect, and include, but are not limited to, compounds of the following classes: isoflavonoids, oligomeric proanthcyanidins, indol-3-carbinol, sulforaphone, fibrous ligands, plant phytosterols, ferulic acid, anthocyanocides, triterpenes, omega 3/6 fatty acids, polyacetylene, quinones, terpenes, cathechins, gallates, and quercitin.

Preferably, dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings for product identification or to characterize the quantity of active compound, (*i.e.*, dosage). Orally formulated compositions of the present invention include, but are not limited to, push-fit capsules (*e.g.*, those made of gelatin), and soft sealed capsules (*e.g.*, those made of

gelatin) optionally having a coating such as glycerol or sorbitol. Push-fit capsules may contain active ingredients mixed with fillers or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol, with or without stabilizers. In preferred embodiments, the pharmaceutically acceptable carriers are preferably pharmaceutically inert.

In preferred embodiments, the pharmaceutical compositions used in the methods of the present invention are manufactured according to well-known and standard pharmaceutical manufacturing techniques (*e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes).

Pharmaceutical compositions suitable for use in the present invention may further include compositions wherein the active ingredient(s) is/are contained in an effective amount to achieve the intended purpose. A therapeutically effective dose refers to that amount of composition(s) that reduces symptoms or eliminates at least one symptom of the disease state. For example, an effective amount of therapeutic compound(s) may be that amount that destroys or disables pathogens as compared to a control.

Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Guidance as to particular dosing considerations and methods of delivery are provided in the literature (*See,* US 4,657,760; 5,206,344; or 5,225,212, all of which are herein incorporated by reference in their entireties). Optimal dosing schedules are calculated from measurements of composition accumulation in the subject's body. The administering physician can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of compositions and can generally be estimated based on the EC_{50} values found to be effective in *in vitro* and *in vivo* animal models. Additional factors that may be taken into account include, but are not limited to, the severity of the disease state the subject's age, weight, and gender; the subject's diet; the time and frequency of administration; combination(s) or agents or compositions; possible reaction sensitivities or allergies; and the subject's tolerance/response to prior treatments. In general, dosage is from 0.001 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly. The treating physician preferably estimates dosing repetition rates based

on measured residence times and concentrations of the agents/drugs in the subject's fluids or tissues. Following successful treatment, it may be desirable to have the subject undergo maintenance therapy to prevent the recurrence of the disease state, wherein the therapeutic agent is administered in maintenance doses, ranging from 0.001 μg to 100 g per kg of body weight, once or more daily, weekly, or other period.

For any pharmaceutical composition used in the methods of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. Then, preferably, dosage can be formulated in animal models (*e.g.*, murine or rat models) to achieve a desirable circulating concentration range.

Toxicity and therapeutic efficacy of administered pharmaceutical compositions can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD_{50} (the dose lethal to 50% of the population) and the ED_{50} (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio LD_{50}/ ED_{50}. Compounds that exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and additional animal studies can be used in formulating a range of dosage, for example, mammalian use (*e.g.*, humans). The dosage of such compounds lies preferably, however the present invention is not limited to this range, within a range of circulating concentrations that include the ED_{50} with little or no toxicity.

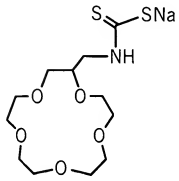
EXPERIMENTAL

The following examples are provided in order to demonstrate and further illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof. In the experimental disclosure which follows, the following abbreviations apply: N (normal); M (molar); mM (millimolar); μM (micromolar); mol (moles); mmol (millimoles); μmol (micromoles); nmol (nanomoles); pmol (picomoles); g (grams); mg (milligrams); μg (micrograms); ng (nanograms); l or L (liters); ml (milliliters); μl (microliters); cm (centimeters); mm (millimeters); μm (micrometers); nm (nanometers); DS (dextran sulfate); and C (degrees Centigrade).

Instruments. Chemicals were purchase from Sigma/Aldrich (St. Louis). ^{1}H NMR spectra were recorded on a 300 MHz Bruker spectrometer. The ^{1}H NMR data were reported as δ(ppm) relative to TMS.

Example I

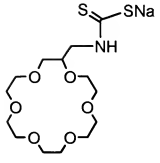
Synthesis of Sodium Dithiocarbamate of 2-Aminomethyl-15-Crown-5



To a cold solution of 2-aminomethyl-15-crown-5 (0.524 g, 2.0 mmol) and sodium hydroxide (0.08 g, 2.0 mmol) in 6 mL of ethanol was added carbon disulfide (0.304 g, 2.0 mmol) dropwise. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h, during which time a white precipitate was formed. Upon addition of 40 mL of diethyl ether vigorous stirring, more precipitate was formed. The mixture was kept still and the supernatant was decanted. The white precipitate was washed twice with ether (2 x 10 mL) and dried under vacuum overnight to give the product as a white solid in quantitative yield. ^{1}H NMR (D_2O, chemical shift δ in ppm): 3.80-3.72(m, 2H), 3.64-3.45(m, 17H), and 3.41(m, 2H). ^{13}C NMR (D_2O, DMSO-d_6 as internal reference, chemical shift δ in ppm): 214.0(C=S), 78.1, 72.0, 71.1, 71.0, 70.8, 70.7, 70.6, 70.5, 70.4, 70.3(crown ether carbons), and 49.4(CH_2N).

Example II

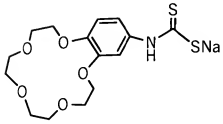
Synthesis of Sodium Dithiocarbamate of 2-Aminomethyl-18-Crown-6



A solution of 2-aminomethyl-18-crown-6 (0.293 g, 1.0 mmol) in 1 mL of ethanol was dropwise added into a cold solution of carbon disulfide (0.076 g, 1.0 mmol) and sodium hydroxide (0.04 g, 1.0 mmol) in 2 mL of ethanol with stirring. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h. Then 30 mL of ether was gradually added with vigorous stirring and the desired dithiocarbamate product was separated as a pale yellow oil, which was further washed twice with ether (2 x 10 mL) and dried under vacuum to give the product as a foamy solid (0.37 g, yield 95%). ^{1}H NMR (D_2O, chemical shift δ in ppm): 3.78(m, 2H), 3.66-3.40(m, 21H), and 3.37(m, 2H). ^{13}C NMR (D_2O, DMSO-d_6 as internal reference, chemical shift δ in ppm): δ 197.0(C=S), 78.5, 72.0, 71.5, 71.0, 70.9, 70.8(m), 70.2, 70.0(crown ether carbons), and 47.7(CH_2N).

Example III

Synthesis of Sodium Dithiocarbamate of 3-Aminobenzo-15-Crown-5

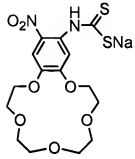


To a cold solution of 4'-aminobenzo-15-crown-5 (0.283 g, 1.0 mmol) and sodium hydroxide (0.04 g, 1.0 mmol) in 5 mL of ethanol was added carbon disulfide (0.076 g, 1.0

mmol) dropwise. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h. Upon addition of 20 mL of diethyl ether with vigorous stirring, a grey precipitate was formed, which was isolated by filtration, washed twice with ether (2 x 10 mL) and dried under vacuum to give the product as a grey solid (0.28 g, yield 74%). ^{1}H NMR (D_2O, chemical shift δ in ppm): 6.73(d, 1H, J = 8.5 Hz), 6.38(d, 1H, J = 2.5 Hz),6.25 (dd, 1H, J = 8.5 and 2.5 Hz), 3.95(m, 4H), 3.70(m, 4H), and 3.60-3.55(m, 8H).

Example IV

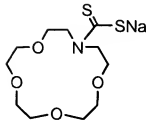
Synthesis of Sodium Dithiocarbamate of 4'-Amino-5'-Nitrobenzo-15-crown-5



To a cold solution of 4'-amino-5'-nitrobenzo-15-crown-5 (0.328 g, 1.0 mmol) and sodium hydroxide (0.04 g, 1.0 mmol) in 5 mL of ethanol was added carbon disulfide (0.076 g, 1.0 mmol) dropwise. Upon addition of the carbon disulfide, a yellow precipitate was formed within 10 min. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h. Upon addition of 20 mL of diethyl ether with vigorous stirring, a golden yellow precipitate was formed, which was isolated by decanting the upper supernatant. Then it was washed twice with ether (2 x 10 mL) and dried under vacuum to give the product as a golden yellow solid (0.41 g, yield 96%). ^{1}H NMR (D_2O, chemical shift δ in ppm): 7.33(s, 1H), 6.25(s, 1H), 4.07-3.95(m, 4H), 3.75(m, 4H), and 3.60-3.53(m, 8H).

Example V

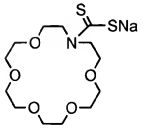
Synthesis of Sodium Dithiocarbamate of 1-Aza- 15-Crown-5



To a cold solution of 2-aminomethyl-15-crown-5 (0.524 g, 2.0 mmol) and sodium hydroxide (0.08 g, 2.0 mmol) in 6 mL of ethanol was added carbon disulfide (0.304 g, 2.0 mmol) dropwise. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h, during which time a white precipitate was formed. Upon addition of 40 mL of diethyl ether vigorous stirring, more precipitate was formed. The mixture was kept still and the supernatant was decanted. The white precipitate was washed twice with ether (2 x 10 mL) and dried under vacuum overnight to give the product as a white solid in quantitative yield. ^{1}H NMR (D_2O, chemical shift δ in ppm): 4.20(t, 4H, J = 6.0 Hz), 3.70(t, 4H, J = 6.0 Hz), and 3.60(m, 12H). ^{13}C NMR (D_2O, DMSO-d_6 as internal reference, chemical shift δ in ppm): 206.1(C=S), 71.2, 70.8, 69.5, and 56.8(crown ether ring carbons).

Example VI

Synthesis of Sodium Dithiocarbamate of 1-Aza- 18-Crown-6

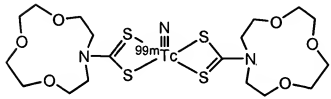


To a cold solution of 1-aza-18-crown-6 (0.276 g, 95%, 1.0 mmol) and sodium hydroxide (0.04 g, 1.0 mmol) in 3 mL of ethanol was added carbon disulfide (0.076 g, 1.0 mmol) dropwise. The resulting mixture was stirred at 0 - 5 °C for another 2 - 3 h. Upon addition of 20 mL of diethyl ether with vigorous stirring, a white precipitate was formed,

which was isolated by decanting the upper supernatant. Then it was washed twice with ether (2 x 10 mL) and dried under vacuum to give the product as a white solid (0.32 g, yield 84%). ^{1}H NMR (D_2O, chemical shift δ in ppm): 4.19(t, 4H, J = 6.0 Hz), 3.70(t, 4H, J = 6.0 Hz), and 3.52(m, 16H). ^{13}C NMR (D_2O, DMSO-d_6 as internal reference, chemical shift δ in ppm): 205.7(C=S), 71.9, 70.9(m), 69.5, 56.7(crown ether ring carbons).

Example VII

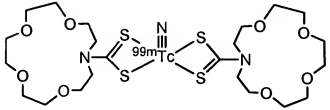
Synthesis of ^{99m}Tc-Nitrido Complex of 1-(Aza-12-Crown-4) Dithiocarbamate



The solution containing succinic dihydrazide (SDH) and propylenediaminetetraacetic acid (PDTA) was prepared according to the literature procedure (Zhang, J. et al. *J. Labelled Compounds & Radiopharm.* 2000, 43: 693-700, herein incorporated by reference). To a 5 mL vial was added the solution containing PDTA (5 mg/mL) and SDH (5 mg/mL), followed by addition of 1.0 mL saline containing 2.0 mCi of ^{99m}Tc-pertechnetate, 10 μL $SnCl_2$ solution in 1.0 N HCl. The reaction mixture was kept at room temperature for 15 min to give the ^{99m}Tc-nitrido intermediate. After addition of 0.5 mL of solution containing sodium 1-(aza-12-Crown-4)-dithiocarbamate (10 mg/mL), the reaction mixture was allowed to stand at room temperature for another 15 min. The radiochemical purity (RCP) was evaluated by radio-HPLC. The retention time was 7.5 min. The RCP was >95%.

Example VIII

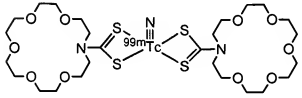
Synthesis of ^{99m}Tc-Nitrido Complex of 1-(Aza-15-Crown-5) Dithiocarbamate



To a 5 mL vial was added the solution containing PDTA (5 mg/mL) and SDH (5 mg/mL), followed by addition of 1.0 mL saline containing 2.0 mCi of ^{99m}Tc-pertechnetate, 10 L $SnCl_2$ solution in 1.0 N HCl. The reaction mixture was kept at room temperature for 15 min to give the ^{99m}Tc-nitrido intermediate. After addition of 0.5 mL of solution containing sodium 1-(aza-15-crown-5)-dithiocarbamate (10 mg/mL), the reaction mixture was allowed to stand at room temperature for another 15 min. The resulting solution was analyzed by radio-HPLC. The retention time was 7.3 min. The RCP was >95%.

Example IX

Synthesis of ^{99m}Tc-Nitrido Complex of 1-(Aza-18-Crown-6) Dithiocarbamate

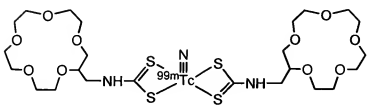


To a 5 mL vial were added the solution containing PDTA (5 mg/mL) and SDH (5 mg/mL), 1.0 mL saline containing 2.0 mCi of ^{99m}Tc-pertechnetate, and 10 μL $SnCl_2$ solution in 1.0 N HCl. The reaction mixture was kept at room temperature for 15 min. After addition of 0.5 mL of solution containing sodium 1-(aza-18-crown-6)-dithiocarbamate (10 mg/mL), the reaction mixture was kept at room temperature for 15 min. The resulting solution was analyzed by radio-HPLC. The retention time was 7.1 min. The RCP was >95%.

Example X

Synthesis of ^{99m}Tc-Nitrido Complex of

N-(1-Aminomethyl-15-Crown-5) Dithiocarbamate.



To a 5 mL vial were added the solution containing PDTA (5 mg/mL) and SDH (5 mg/mL), 1.0 mL saline containing 2.0 mCi of ^{99m}Tc-pertechnetate, and 10 μL $SnCl_2$ solution in 1.0 N HCl. The reaction mixture was kept at room temperature for 15 min. After addition of 0.5 mL of solution containing sodium N-(1-aminomethyl-15-Crown-5)-dithiocarbamate (10 mg/mL), the reaction mixture was kept at room temperature for 15 min. The resulting solution was analyzed by radio-HPLC. The retention time was 7.4 min. The RCP was >95%.

Example XI

In Vivo Testing

The compounds of the present invention may be tested in vivo to determine the therapeutic characteristics of these compounds and to identify particular compounds with the desired characteristics. For example, animal studies may be performed following the literature procedures (e.g., Boschi, A. et al *Nucl. Med. Commun.* 2002, 23: 689, herein incorporated by reference). Biodistribution studies may be carried out using Sprague-Dawley rats in compliance with NIH animal experiment guidelines (*Principles of Laboratory Animal Care*, NIH Publication No. 86-23, revised 1985). One objective of these studies is to determine the characteristics of the ^{99m}Tc complexes (or other compounds of the present invention) as radiopharmaceuticals. These studies may be used as a preliminary screening tool to determine the biodistribution characteristics, excretion kinetics, and metabolism of ^{99m}Tc complexes of crowned DTC chelators.

Sprague-Dawley rats (200 – 250 g) may be anesthetized with an intramuscle injection of a mixture of ketamine (80 mg/kg) and xylazine (19 mg/kg). These rats may then receive the ^{99m}Tc radiopharmaceutical (50 – 100 μCi in 100 μL solution) via intravenous injection into the tail vein. The amount of activity administered to each animal may be quantified, ultimately allowing the biodistribution of each radiopharmaceutical to be calculated as both a percentage of the injected dose per organ (%ID/organ) and a percentage of the injected dose per gram of tissue wet mass (%ID/g). The animals may then be sacrificed via exsanguinations and opening of thoracic cavity at selected time points. Relevant tissues and organs may then be excised, weighed, and counted to determine the tissue uptake of the ^{99m}Tc complex (or other compounds of the present invention that are tested). The organs that may be examined include, for example, heart, brain, blood, lung, liver, spleen, kidneys, muscle, intestines, and bone. Five rats, for example, may be used at each selected time point

to ensure acquisition of reliable biological data. Statistical analysis of the biodistribution data from these experiments may employ the Student *t* test for comparison of radiotracer biodistribution between different ^{99m}Tc radiopharmaceuticals (or other compounds of the present invention). For comparison purpose, biodistribution studies may also performed on both ^{99m}Tc-Sestamibi and ^{99m}Tc-Tetrofosmin, which are two radiopharmaceuticals approved for myocardial perfusion imaging. Preferred ^{99m}Tc radiopharmaceuticals would be those, which have high heart uptake, long heart retention time, and rapid blood clearance, preferably via renal system.

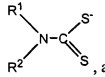
This model can also be used to assess the effectiveness of radiopharmaceuticals of the present invention comprised of a positron emitting isotope such as ^{94m}Tc. The radiopharmaceuticals may be administered in appropriate amounts and the uptake in the heart can be quantified non-invasively by imaging for those isotopes with a coincident imageable gamma emission. The diagnostic radiopharmaceuticals may be administered by intravenous injection, usually in saline solution, at a dose of 1 to 100 mCi per 70 kg body weight, or preferably at a dose of 5 to 30 mCi. Imaging is performed using known procedures. The therapeutic radiopharmaceuticals may be administered by intravenous injection, usually in saline solution, at a dose of 0.1 to 100 mCi per 70 kg body weight, or preferably at a dose of 0.5 to 50 mCi per 70 kg body weight.

All publications and patents mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described method and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry or related fields are intended to be within the scope of the following claims.

We Claim:

1. A composition comprising a compound comprising the following formula: $(M{\equiv}N)L^1$ and pharmaceutically acceptable salts thereof;
wherein N is Nitrogen;
wherein M is a transition metal; and
wherein L^1 is a first crowned dithiocarbamate, wherein said first crowned dithiocarbamate comprises a first crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2.

2. The composition of Claim 1, wherein said first crowned dithiocarbamate comprises the following formula:



, and pharmaceutically acceptable salt thereof, wherein R^1 or R^2 comprise said first crown ether-containing group, or R^1 and R^2 together comprise said first crown ether-containing group.

3. The composition of Claim 1, wherein said transition metal is a radioactive metal.

4. The composition of Claim 1, wherein said transition metal is ^{99m}Tc or ^{94m}Tc.

5. The composition of Claim 1, wherein said transition metal is ^{186}Re or ^{188}Re.

6. The composition of Claim 1, wherein subscript a in said formula of said first crown ether-containing group is 2, 3, 4, or 5.

7. The composition of Claim 1, wherein subscript a in said formula of said first crown ether-containing group is 2 or 3.

8. The composition of Claim 1, wherein subscript a in said formula of said first crown ether-containing group is 2.

9. The composition of Claim 1, wherein subscript b in said formula of said first crown ether-containing group is 3, 4, 5, 6, 7, or 8.

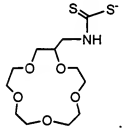
10. The composition of Claim 1, wherein subscript b in said formula of said first crown ether-containing group is 3, 4, 5 or 6.

11. The composition of Claim 1, wherein subscript c in said formula of said first crown ether-containing group is 2, 3, 4, or 5.

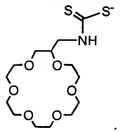
12. The composition of Claim 1, wherein subscript c in said formula of said first crown ether-containing group is 2 or 3.

13. The composition of Claim 1, wherein subscript c in said formula of said first crown ether-containing group is 2.

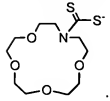
14. The composition of Claim 1, wherein said first crowned dithiocarbamate is



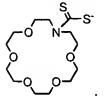
15. The composition of Claim 1, wherein said first crowned dithiocarbamate is



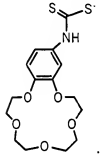
16. The composition of Claim 1, wherein said first crowned dithiocarbamate is



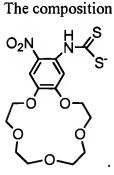
17. The composition of Claim 1, wherein said first crowned dithiocarbamate is



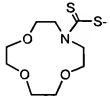
18. The composition of Claim 1, wherein said first crowned dithiocarbamate is



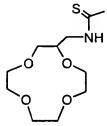
19. The composition of Claim 1, wherein said first crowned dithiocarbamate is



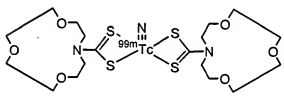
20. The composition of Claim 1, wherein said first crowned dithiocarbamate is selected from



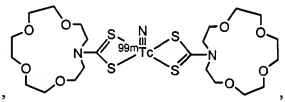
, and



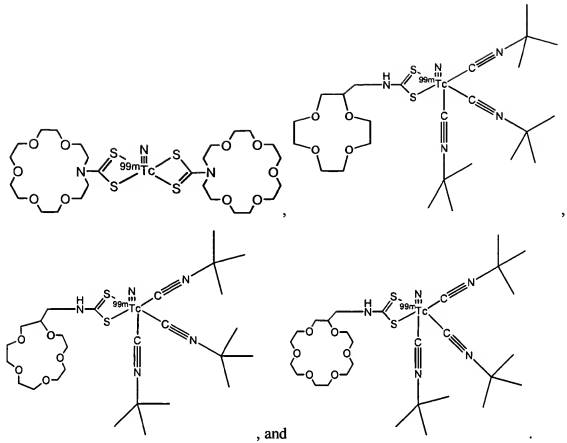
21. The composition of Claim 1, wherein said compound is selected from the group consisting of:



,



,



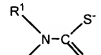
, and

22. The composition of Claim 1, wherein said compound further comprises L^2 and comprises the following formula:

$(M{\equiv}N)L^1L^2$ and pharmaceutically acceptable salts thereof;

wherein L^2 is a second crowned dithiocarbamate, wherein said second crowned dithiocarbamate comprises a second crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2.

23. The composition of Claim 22, wherein said second crowned dithiocarbamate comprises the following formula:



, and pharmaceutically acceptable salt thereof, wherein R^1 or R^2 comprise said second crown ether-containing group, or R^1 and R^2 together comprise said second crown ether-containing group.

24. The composition of Claim 22, wherein subscript a in said formula of said second crown ether-containing group is 2, 3, 4, or 5.

25. The composition of Claim 22, wherein subscript a in said formula of said second crown ether-containing group is 2 or 3.

26. The composition of Claim 22, wherein subscript a in said formula of said second crown ether-containing group is 2.

27. The composition of Claim 22, wherein subscript b in said formula of said second crown ether-containing group is 3, 4, 5, 6, 7, or 8.

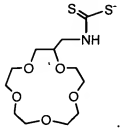
28. The composition of Claim 22, wherein subscript b in said formula of said second crown ether-containing group is 3, 4, 5 or 6.

29. The composition of Claim 22, wherein subscript c in said formula of said second crown ether-containing group is 2, 3, 4, or 5.

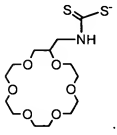
30. The composition of Claim 22, wherein subscript c in said formula of said second crown ether-containing group is 2 or 3.

31. The composition of Claim 22, wherein subscript c in said formula of said second crown ether-containing group is 2.

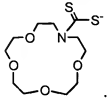
32. The composition of Claim 22, wherein said second crowned dithiocarbamate is



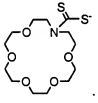
33. The composition of Claim 22, wherein said second crowned dithiocarbamate is



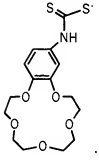
34. The composition of Claim 22, wherein said second crowned dithiocarbamate is



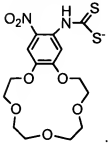
35. The composition of Claim 22, wherein said second crowned dithiocarbamate is



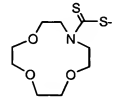
36. The composition of Claim 22, wherein said second crowned dithiocarbamate is



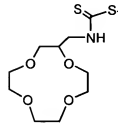
37. The composition of Claim 22, wherein said second crowned dithiocarbamate is



38. The composition of Claim 22, wherein said second crowned dithiocarbamate is selected from

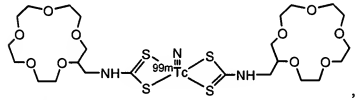


, and

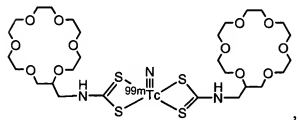


.

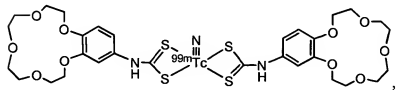
39. The composition of Claim 1, wherein said compound is selected from the group consisting of:



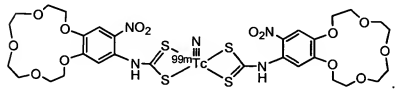
,



,

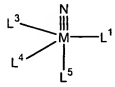


, and



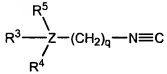
.

40. The composition of Claim 1, wherein said compound further comprises L^3, L^4, and L^5 and comprises the following formula:



and pharmaceutically acceptable salts thereof;

wherein L^3, L^4, and L^5 each comprise an isonitrile of the following formula:



wherein q is 0 – 3;

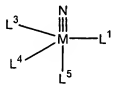
Z is carbon or silicon;

R^3, R^4 and R^5 are the same or different, and are selected from: H, C_1-C_{10} alkyl substituted with 0 - 5 R^6, aryl substituted with 0-5 R^6, heteroaryl substituted with 0-5 R^6, and macrocyclic crown ether containing 2 – 8 ether-oxygen atoms;

wherein R^6 is selected from: H, OH, OR^7, $C(=O)OR^7$, $C(=O)NR^8R^9$, $PO(OR^8)_2$, $PO(NR^8R^9)_2$ and SO_2R^7;

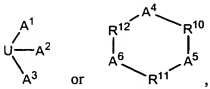
R^7, R^8 and R^9 are same or different, and are selected from: H, alkyl, aryl, and heteroaryl, or R^8 and R^9 together form a macrocyclic crown ether containing 2 – 8 ether-oxygen atoms.

41. The composition of Claim 1, wherein said compound further comprises L^3, L^4, and L^5 and comprises the following formula:



and pharmaceutically acceptable salts thereof;

wherein L^3, L^4, and L^5 together form a tripodal chelator with the following formula:

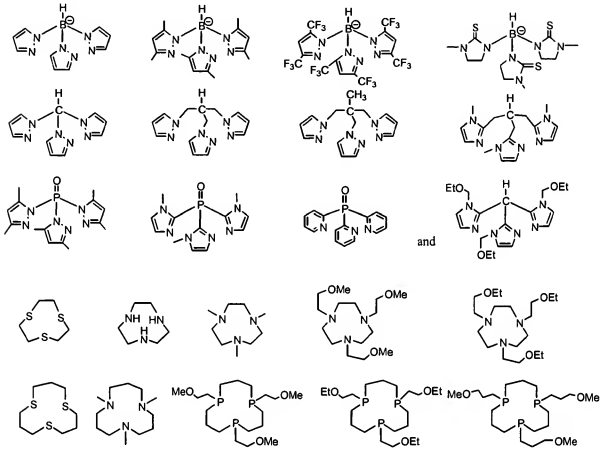


or

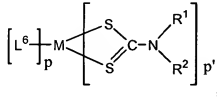
, wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles; A^4, A^5 and A^6 are selected from: NR^{14}, PR^{14}, S, and O; R^{10}, R^{11} and R^{12} are selected from a group of the formula:

$-(CH_2)_g-$, wherein g is 2 – 5; R^{13} is selected from: H, alkyl and aryl group; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl.

42. The composition of Claim 41, wherein said tripodal chelator is selected from



43. A composition comprising a compound comprising the following formula:



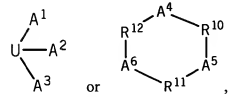
, and pharmaceutically acceptable salt thereof,

wherein M is a transition metal selected from: Fe(II), Fe(III), Mn(II), Mn(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ru(II), Ru(III), Pd(II), and Pt(II);

p and p' are integers and are independently selected from 0 – 2;

R^1 and R^2 comprises a crown ether-containing group of the following formula: $[(CH_2)_a-O]_b-(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2, or wherein R^1 and R^2 together comprise said crown ether-containing group;

wherein L^6 is a tripodal chelator with a formula selected from:



or , wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles;

A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S;

R^{10}, R^{11} and R^{12} are selected from a group of the formula: $-(CH_2)_g-$,

wherein g is 2 – 5;

R^{13} is selected from: H, alkyl and aryl group; and

R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl.

44. A method for radioimaging a subject comprising;

a) providing;

i) a subject, and

ii) a composition comprising a compound comprising the following formula: $(M\equiv N)L^1$ and pharmaceutically acceptable salts thereof;

wherein N is Nitrogen; wherein M is a radioactive transition metal; and wherein L^1 is a first crowned dithiocarbamate, wherein said first crowned dithiocarbamate comprises a first crown ether-containing group of the following formula: $[(CH_2)_a-O]_b-(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2;

b) administering said composition to said subject, and

c) scanning at least a portion of said subject using a radioimaging device.

45. The method of Claim 44, wherein at least a portion of said subject is tissue suspected of being diseased.

46. The method of Claim 44, wherein said at least a portion of said subject is myocardial tissue.

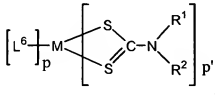
47. The method of Claim 44, wherein said subject is a mammal.

48. A method of treating a disease resulting from overproduction of nitric oxide or reactive oxygen species, comprising;

a) providing;

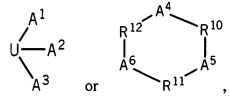
i) a subject with a disease, and

ii) a composition comprising a compound comprising the following formula:



,

and pharmaceutically acceptable salt thereof, wherein M is a transition metal selected from: Fe(II), Fe(III), Mn(II), Mn(III), Co(II), Co(III), Ni(II), Cu(II), Zn(II), Ru(II), Ru(III), Pd(II), and Pt(II); p and p' are integers and are independently selected from 0 – 2; R^1 and R^2 comprises a crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2, or wherein R^1 and R^2 together comprise said crown ether-containing group; wherein L^6 is a tripodal chelator with a formula selected from:



, wherein U is selected from a group: $R^{13}B$, CR^{13}, and P(=O); A^1, A^2 and A^3 are imine-N containing heterocycles; A^4, A^5 and A^6 are selected from: NR^{10}, PR^{10}, and S; R^{10}, R^{11} and R^{12} are selected from a group of the formula: $-(CH_2)_g-$, wherein g is 2 – 5; R^{13} is selected from: H, alkyl and aryl group; and R^{14} is selected from: H, alkyl, aryl, and alkoxyalkyl; and

b) administering said composition to said subject.

49. A method of treating metal poisoning, comprising;

a) providing;

i) a subject with metal poisoning, and

ii) a composition comprising a crowned dithiocarbamate, wherein said crowned dithiocarbamate comprises a crown ether-containing group of the following formula: $[(CH_2)_a\text{-}O]_b\text{-}(CH_2)_c$, wherein a is at least 2, b is at least 3, and c is at least 2; and

b) administering said composition to said subject.

Abstract

The present invention provides compositions comprising crowned dithiocarbamate metal complexes and methods of using these compositions. In particular, the present invention provides neutral and cationic radioactive metal-nitrido complexes of crowned dithiocarbamates (DTCs), and methods of using these complexes as radiopharmaceuticals for diagnosis and treatment of cardiovascular disorders, infectious disease, and cancer. The present invention also provides tripodal chelator-metal complexes of crowned DTCs and methods of using these complexes for treating diseases such as those characterized by nitric oxide overproduction. The present invention further provides methods of using crowned DTCs for heavy metal detoxification.